# Gestational Diabetes Mellitus in North India. Prevalence, Diagnostic Criteria, Pathophysiological Aspects and Genetic and Non-Genetic Origin in the State of Punjab.

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## Prevalence, Diagnostic Criteria, Pathophysiological Aspects and Genetic and Non-Genetic Origin in the State of Punjab

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LUND
UNIVERSITY

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Title and subtitle
Gestational Diabetes Mellitus in North India - Prevalence, Diagnostic Criteria, Pathophysiological Aspects and Genetic and Non-Genetic Origin in the State of Punjab.


Abstract
Gestational diabetes mellitus(GDM) defines an unhealthy state of hyperglycaemia that develops in response to an otherwise normal physiological adaptive insulin resistance state during pregnancy. However, the exact plasma glucose levels differentiating the unhealthy GDM state from a normal pregnancy is unknown, and relies upon arbitrary cut off criteria based on associations with adverse health outcomes in mother and child. The normal hormonal and physiological changes during pregnancy and difficulties in assessing long term health outcomes associated with GDM in mother and child is a further complicating factor. Ethnic differences plays a major role in defining GDM with Asian people developing diabetes including GDM at a lower degree of overweight compared with non-Asian people. Epidemiological data points towards Asia as the present and future hub of diabetes. The thesis is based upon results obtained from the first state-of-the art epidemiological screening of 5000 women for GDM in Punjab, North India, using former WHO1999 compared with adapted WHO2013 criteria.
The work documents that the proposed WHO2013 criteria increases the prevalence of GDM in North India from 9% using former criteria to include no less than 35% of all pregnant women. It documents a key role of impaired insulin secretion as opposed to peripheral insulin resistance in the pathyphysiology of GDM, and it shows that a myriad of risk factors including family history of diabetes, age, BMI, diet, religion, illeteracy and urban versus rural habitat influences risk of GDM, as well as impaired insulin secretion and action, in a hitherto unrecognized complex manner.
Importantly, genetic analyses of 79 SNPs previously associated with type 2 diabetes (including 12 GDM loci), in Indian and non-Indian populations suggests that genetic as well as non-genetic origin of GDM in North India differ from other ethnic populations. Only few of the previously reported diabetes risk genes were associated with risk of GDM, some showed nominal significance and some associations in opposite directions, being protective against GDM in North India. The results underscores the need for large prospective studies of GDM women and their offspring in different ethnic groups to understand the quantitative and qualitative adverse health outcomes, diagnostic criteria as well as the need, tools and targets for prevention and treatment in a life-cycle perspective.



Key words Gestational dabetes mellitus, oral glucose tolerance test,type 2 diabetes,prevalence, diagnostic criteria, genetic variant, ethnic groups, insulin secretion, insulin resistance

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# Gestational Diabetes Mellitus in North India

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*“One night I dreamed a dream.*
*As I was walking along the beach with my Lord.*
*Across the dark sky flashed scenes from my life.*
*For each scene, I noticed two sets of footprints in the sand,*
*One belonging to me and one to my Lord.*
*After the last scene of my life flashed before me,*
*I looked back at the footprints in the sand.*
*I noticed that at many times along the path of my life,*
*especially at the very lowest and saddest times,*
*there was only one set of footprints.*
*This really troubled me, so I asked the Lord about it.*
*"Lord, you said once I decided to follow you,*
*You'd walk with me all the way.*
*But I noticed that during the saddest and most troublesome times of my life,*
*there was only one set of footprints.*
*I don't understand why, when I needed You the most, You would leave me."*
*He whispered, "My precious child, I love you and will never leave you*
*Never, ever, during your trials and testings.*
*When you saw only one set of footprints,*
*It was then that I carried you.”*

Margaret Fishback Powers, 1964

*To my family & A tribute to my mother (Late) Professor Nita Puri*

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# List of Publications

*Publications included in this thesis*

Paper I — Arora GP, Thaman RG, Prasad RB, Almgren P, Brøns C, Groop LC, Vaag AA. Prevalence and risk factors of gestational diabetes in Punjab, North India: results from a population screening program. *Eur J Endocrinol.* 2015 Aug;1 73(2):257-67.

Paper II — Arora GP, Almgren P, Thaman RG, Pal A, Groop L, Vaag A, Prasad RB, Brøns C. Insulin Secretion and Action in North Indian Women during Pregnancy. *Diabetic Medicine*2017 Jul 21. (Epub ahead of print)

Paper III — Arora GP, Almgren P, Brøns C, Thaman RG, Vaag AA, Groop L, Prasad RB. Association of Genetic Risk Variants and Glucose Intolerance during Pregnancy in a North Indian Population (to be submitted).

Paper IV — Arora GP, Åkerlund M,Brøns C,Almgren C, Thaman RG, Berntorp K, Vaag AA, Groop L,PrasadRB. Phenotypic and Genotypic differences between Indian and Swedish women with gestational diabetes mellitus (to be submitted).

# Publications not included in the thesis

- Vaag A, Arora GP, Thaman RG. Timing of intergenerational prevention of adiposity and Type 2 Diabetes Mellitus. J Physiol. 2012 Mar;590 ( 5):1021-2.
- Vaag AA, Grunnet LG, Arora GP, Brøns C. The thrifty phenotype hypothesis revisited. Diabetologia 2012 Aug; 55(8): 2085-2088.
- Thaman RG, Arora GP. Metabolic Syndrome: Definition and Pathophysiology – the discussion goes on! J Phys Pharm Adv. 2013; 3(3): 48-56.
- Vaag A, Brøns C, Gillberg L, Hansen NS, Hjort L, Arora GP, Thomas N, Broholm C, Ribel-Madsen R, Grunnet LG. Genetic, non-genetic and epigenetic risk determinants in developmental programming of type 2 diabetes. Acta Obstet Gynecol Scand. 2014 Nov;93 (11):1099-108.
- Marseille E, Lohse N, Jiwani A, Hod H, Seshiah V, Yajnik CS, Arora GP, Balaji V, Henriksen O, Lieberman N, Chen R, Damm P, Metzger BE, Kahn JG, The cost-effectiveness of gestational diabetes screening including prevention of type 2 diabetes: application of a new model in India and Israel.JMatern Fetal Neonatal Med. 2013 Feb;26 (8), 802-810.
- Thaman RG, Girgla KK, Arora GP. Circadian peak expiratory flow rate variability in healthy North Indian geriatric population. Journal, Indian Academy of Clinical Medicine. 2010 Sep;11 (3): 195-8.
- Banshi Saboo, Ravinder Garg, Geeti Puri Arora “Glycemic variability and glucosidase inhibitor” in medical update: Progress in medicine 2016, Vol 1. Sec 1,Page 45-48.

# Abbreviations

| | |
|---|---|
| ADA | American Diabetes Association |
| ANOVA | Analysis of variance |
| BMI | Body mass index |
| CPG | Capillary plasma glucose |
| CI | Confidence interval |
| CV | Coefficient of variation |
| DIPSI | Diabetes in Pregnancy Study group in India |
| DNA | Deoxyribonucleic acid |
| EASD | European Association for the Study of Diabetes |
| GDM | Gestational Diabetes Mellitus |
| GRS | Genetic risk scores |
| FPG | Fasting plasma glucose |
| HOMA-B | Homeostatic Model Assessment - beta cell function |
| HOMA-IR | Homeostatic Model Assessment - insulin resistance |
| IFG | Impaired fasting glucose |
| IADPSG Study Group | International Association of Diabetes and Pregnancy |
| IDF | International Diabetes Federation |
| IGT | Impaired glucose tolerance |
| OGTT | Oral glucose tolerance test |
| OR | Odds ratio |
| PG | Plasma glucose |
| PNGT | Pregnant normal glucose tolerance |
| PRS | Polygenic risk scores |
| SD | Standard deviation |
| SNP | S*ingle-nucleotide polymorphism* |
| T1D | Type 1 diabetes |
| T2D | Type 2 diabetes |
| VPG | Venous plasma glucose |
| WHO | World Health Organization |

# Populärvetenskaplig sammanfattning

Graviditetsdiabetes i Norra Indien (Punjab) – förekomst, diagnostiska kriterier samt genetiska och icke-genetiska orsaker.

Graviditetsdiabetes (GDM) innebär ett ohälsosamt tillstånd med förhöjt blodsocker under graviditet som förvärrar den annars fysiologiska insulinresistensen som utvecklas under en graviditet. Vår kunskap om exakt vilken blodsockernivå som skiljer det ohälsosamma GDM-tillståndet från en normal graviditet är emellertid begränsad och baserad på arbiträra gränsvärden som associerats med ökade hälsorisker hos mor och barn. Hur de normalt förkommande hormonella och fysiologiska förändringar som sker under graviditeten påverkar hälsan hos mor och barn är bara delvis kända. Etniska skillnader kan spela en stor roll. Exempelvis utvecklar asiater typ 2 diabetes (T2D) och GDM vid en lägre grad av övervikt än européer. Alla prognoser tyder på att Asien kommer att se en explosionsartad ökning i förekomst av T2D och GDM. Den här avhandlingen behandlar problematiken kring GDM i Asien och bygger på en epidemiologisk screening av 5000 gravida kvinnor i Punjab i Norra Indien. För diagnos av GDM användes såväl WHO 1999 som WHO 2013 definitioner.

WHO 2013 kriterierna ökar förekomsten av GDM från 9% (WHO1999) till 35% av alla gravida kvinnor. Insulinbrist spelar en större roll än insulinresistens i GDM patofysiologin. Därutöver spelar ett antal riskfaktorer såsom ärftlighet för T2D, ålder, kroppsindex (BMI), kost, religion, analfabetism och om man bor i stad eller på landsbygd en avgörande roll för risken att diagnostiseras med GDM.

En analys av 79 genvarianter som tidigare visats vara associerade med T2D och GDM (12 av dem i Indien) visade på klara skillnader i genetiska och icke-genetiska orsaker till GDM mellan indiska kvinnor och kvinnor från Sverige. Endast ett fåtal av de tidigare kända riskvarianterna var förenade med ökad risk för GDM i Indien. En av genvarianterna som associerats med ökad risk för GDM i andra populationer var skyddande för GDM i den aktuella populationen.

Sammanfattningsvis understryker resultaten behovet av ytterligare större prospektiva undersökningar av kvinnor med GDM och deras barn i olika etniska grupper för att förstå det komplexa sambandet mellan riskfaktorer och hälsorisker i olika delar av världen. Vi behöver också bättre förstå kopplingen mellan diagnostiska kriterier och hälsorisker för mor och barn samt utveckla bättre redskap för att förhindra att GDM uppstår.

# Abstract

Gestational diabetes mellitus (GDM) defines an unhealthy state of hyperglycemia that develops in response to an otherwise normal physiological adaptive insulin resistance state during pregnancy. The exact plasma glucose levels differentiating the unhealthy GDM state from a normal pregnancy are unknown, and based upon arbitrary cut off criteria defined by adverse health outcomes in the mother and child. The normal hormonal and physiological changes during pregnancy as well as the difficulties in assessing long term health outcomes in both the mother and child associated with GDM is a further complicating factor defining the diagnostic criteria. To this end, ethnic differences play a major role in defining GDM with Asian people in general developing diabetes and GDM at lower body mass index (BMI) than non-Asian people. Indeed, epidemiological data and forecasts identify Asia as the present and future hub of diabetes. The current thesis is based upon results obtained from the first state-of-the art epidemiological screening program of 5000 pregnant women for GDM in Punjab, North India, using both WHO1999 and WHO2013 criteria.

The thesis demonstrates that the proposed WHO2013 criteria increase the prevalence of GDM in North India from 9% using former WHO1999 criteria to 35% of all pregnant women. Environmental risk factors influenced GDM differently depending upon the criteria applied for the diagnosis of GDM. Urban habitat, illiteracy, non-vegetarianism, increased BMI, Hindu religion and low adult height were independent risk factors for GDM using the 1999 criteria, whereas only urban habitat, low adult height and increased age were independent risk factors of GDM using the 2013 criteria. The thesis also demonstrated a key role for impaired insulin secretion in the pathophysiology of GDM in North India. Importantly, a myriad of risk factors including family history of diabetes, age, BMI, diet, religion, illiteracy and urban versus rural habitat influences risk of GDM together with impaired insulin secretion and action, in a hitherto unrecognized complex manner. GDM defined using both criteria was associated with reduced insulin secretion compared to pregnant normal glucose tolerance women. Women classified as GDM by the WHO2013 criteria exhibit lower insulin secretion and are more insulin resistant than women classified as GDM using the GDM1999 criteria. The thesis also showed that non-genetic risk factors for GDM influence insulin secretion and action in North Indian women differently from other populations. Urban habitat, illiteracy, high age and low BMI were independently associated with reduced insulin secretion whereas Sikh religion, increasing age and BMI, as well as family history of diabetes were independently associated with increased insulin resistance.

The thesis furthermore analyzed the genetic framework of GDM in this North Indian pregnant cohort. We analyzed a total of 79 SNPs previously reported to be

associated with T2D, GDM (12 SNPs) and/or glycemic traits in Indian and non-Indian populations. The data demonstrated that the genetics of GDM in North India differs significantly from other ethnic populations. Notably, the risk allele T of SNP rs5219 of in the*KCNJ11*gene (WHO1999) as well as, variants in the *GRB14* (WHO1999), *SLC2A2* (WHO2013) genes, criteria used are presented within brackets. In contrast, T2D risk variants in the *CRY2* (WHO1999), *CENTD2* (WHO2013) and *ADCY5* (WHO2013) genes were associated with reduced risk of GDM. In general, effect of genetic variants was more pronounced using WHO1999 than WHO2013 criteria as clearly shown for the most significant *TCFL2* risk variant *TCF7L2*. We also explored phenotypic and genetic differences between pregnant women with GDM from India and Sweden and showed that Indian women had higher prevalence of GDM (compared to previous reports), lower insulin secretion and better insulin sensitivity than Swedish women. The rs7178572 SNP in the *HMG20A* gene previously associated with T2D GDM in India was also here nominally associated with GDM in Indian but not in Swedish women. The T2D risk SNP rs11605924 in the *CRY2* gene was associated with GDM in both populations, but in opposite directions; the same allele was associated with increased risk of GDM in Swedish but decreased risk in Indian women.

Since the current criteria are based upon health consequences for women and the child both, it would be important in future studies to also explore the potential genetic influences on adverse health outcome in the offspring.

# Introduction

## History

Egyptian medicine dates back to year 2900 BC. A well-preserved papyrus found by archaeologists in an ancient grave in Thebes turned out to be an ancient textbook of medicine. The papyrus, named after the German Egyptologist George Ebers, was written around 1550 BC and is considered one of the most famous documents related to ancient practice of medicine. The papyrus describes a condition that resembles diabetes by the phrase "to eliminate urine which is too plentiful"(1). The term diabetes was first used by the Greek Apollonius of Memphis around 230 BC and means to pass through (dia - through, betes - to go)(2). Another Greek physician Aretaeus of Cappadocia described around 150 AD this condition as "the melting down of flesh and limbs into urine" (3). Terms like "wasting disorder" or "excessive thirst disorder" related to untreated diabetes mellitus have also been used in the literature (4).

Diabetes is also known by the name "Madhumeha" in India, meaning honeyed urine. Type 1 diabetes (T1D) and type 2 diabetes (T2D) were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 5$^{th}$ century AD, withT1D associated with youth and T2D with obesity(5).

In recent times, the first case of a woman with diabetes during pregnancy was recorded in 1823 by a German physician Heinrich Bennewitz in his thesis "De DiabeteMellito Graviditatis Symptomate" (6). Later, Mathew Duncan reported an increased risk of fetal death complicated by diabetes (7). At that time, it was believed that diabetes was a symptom of pregnancy (6), including glycosuria, increased thirst and polyuria, which disappeared after pregnancy (8). Studies revealed that abnormal glucose tolerance was responsible for increased perinatal mortality in infants born to mothers who subsequently developed diabetes as reported in 1940 (9-13).

It was Jackson and Hoet who articulated the concept of gestational diabetes as we understand it today (14). The term gestational diabetes was first used by O'Sullivan in 1961 (15) and was revisited by Hadden in 1975(16) and later used at an international conference in 1979 (17). In 1964, O'Sullivan and Mahan reported that pregnant women with glucose values in the upper end of the spectrum were more

likely to develop diabetes later in life, and that it was the added stress of pregnancy that revealed the women's "pre-diabetic status". In the decades thereafter, the concept of glucose intolerance during pregnancy has been extensively studied, and has resulted in an official diagnostic definition namely gestational diabetes mellitus (GDM).

# Definition

The first definition of GDM was proposed by O' Sullivan in 1961as "Carbohydrate intolerance of variable severity with onset or first recognition during pregnancy", irrespective of whether or not insulin is used for treatment or the condition persists after pregnancy (18). Furthermore, it included the possibility that the glucose intolerance may have antedated the pregnancy (Second Int. Workshop Conference, 1985) (2-18,19-22). The re-defined GDM diagnosis by WHO in 1999 was "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy" (22).

Even though there have been subsequent proposals for changes of terminology to define GDM, the WHO 1999 definition was applied in the present study. In 2013, a modified definition was proposed by WHO defining GDM as "hyperglycemia first time detected at any time during pregnancy"(23). Lower glucose concentrations are used as diagnostic criteria for GDM as compared to diagnostic criteria used in non-pregnant states, the rationale for this being an increased risk of adverse pregnancy outcomes for both the mother and the child. The most recent (2017) definition of GDM is by the American Diabetes Association defining GDM as "diabetes diagnosed in second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation"(24). The fact that the definition of GDM continues to be updated reflects the many uncertainties there are with respect to GDM being defined as a disease entity, and there is a high need for a uniform and standardized definition to diagnose GDM in a population that accurately reflects its associated risks in both mother and child. Indeed, there remains no doubt, that the identification of pregnant women with diabetes, and subsequent treatment, is required to reduce maternal and infant morbidity and mortality as well as adverse perinatal outcomes (25). The question however, of which disease criteria as well as treatment goals and modalities to be used, remains uncertain and may differ between different ethnic groups and societies.

# Epidemiology of GDM

According to International Diabetic Federation (IDF) Atlas from 2015, there are 415 million adults between 20-79 years of age with diabetes worldwide (29). This figure includes 193 million of undiagnosed cases. The global prevalence of diabetes was 4% in 1995, which may increase to 5.4% by year 2025, making it 642 million by 2040 (29) and by the same year the number of individuals diagnosed with diabetes residing in developing countries will increase from 62% in 1995 to almost 75% (29). In India there are approximately 69 million people with diabetes, and according to predictions from the WHO, developing countries like India are bound to bear the majority of the diabetes epidemic in the 21st century (rise estimated to 80 million diabetics by year 2030) (Fig. 1). As shown in the figure below (Fig.2), GDM represents around 90% of all pregnancies complicated by diabetes {26}, and it is well accepted that women diagnosed with GDM have an increased risk of future diabetes {27}. GDM represents primary prevention level to evaluate and possibly prevent Type 2 diabetes in two generations {28}.

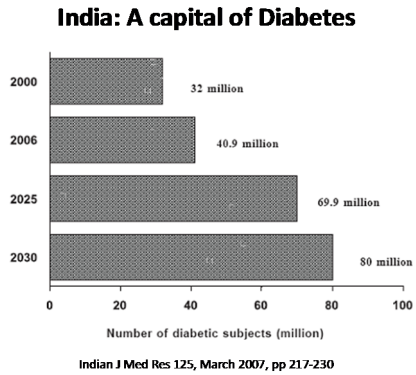



**Figure 1**

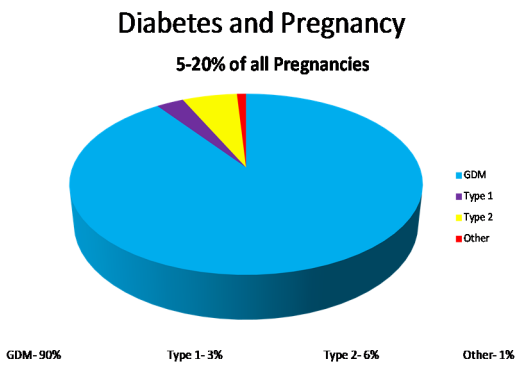



**Figure 2.** Diabetes in pregnancy. Contribution of GDM, Type 1 and Type 2 diabetes(26)

The prevalence of GDM differs in ethnic groups and in particular with the use of different diagnostic criteria. Among Caucasians using earlier than the WHO2013 criteria, the prevalence is approximately 2-4% as compared to 5-10% in the Asian population, 5-7% in Hispanic/Mexican Americans and 5-7% in the Arab population (30-52). For the same degree of obesity, Indian women are known to have a much higher prevalence of diabetes, and the relative risk of developing GDM in South Indian women has been also reported to be 11.3 times that of Caucasian women

(53). Presently, India has about 20 million women in the reproductive age between 20 and 39 years, and the prevalence of GDM in India was reported to be 17% in 2000 (South Indian women)(54,55). Notably, the diversity of the Indian population is among the greatest in the world, the reasons being multifactorial including both genetics and non-genetic differences between the Northern and Southern parts of India. However, studies on the prevalence of GDM in North Indian women have been sparse, at least before the work of the current thesis was initiated.

# Pathophysiology of GDM

*Normal glucose metabolism in pregnancy*

The flow of maternal nutrients across placenta during the nine months of pregnancy ensures normal development and growth of the fetus. In pregnancy, glucose is the main source of fetal energy (56). Glucose is transported passively across the placenta in a concentration dependent manner (57). Early in gestation, the pancreatic beta cells of fetus are relatively insensitive to glucose and are characterized by a relatively high basal insulin secretion rate. During the second half of gestation, more glucose molecules are passing through the placenta to meet the demands of the growing fetus (58). This gradually results in a shift of the placenta concentration gradient and a decrease of glucose in the maternal circulation. As a consequence of this, the placenta is thought to release hormones that increase insulin resistance and hepatic glucose production in the mother, thereby ensuring the placental glucose gradient at a level sufficient for the fetus to keep growing (59). The increased insulin resistance in the mother during the last two trimesters is counter balanced by a compensatory increase in insulin secretion keeping them euglycemic. (60,61). Thus, it is well known that pancreatic beta cells can proliferate both in- and outside pregnancy to maintain near normal plasma glucose level even when insulin action is reduced(62). During pregnancy, maternal insulin resistance further ensures that nutrients are directed towards the fetus and not stored as glycogen in the muscle or liver of the mother. It has been suggested that women with GDM exhibit a defect in the placental-beta-cell-axis (63).

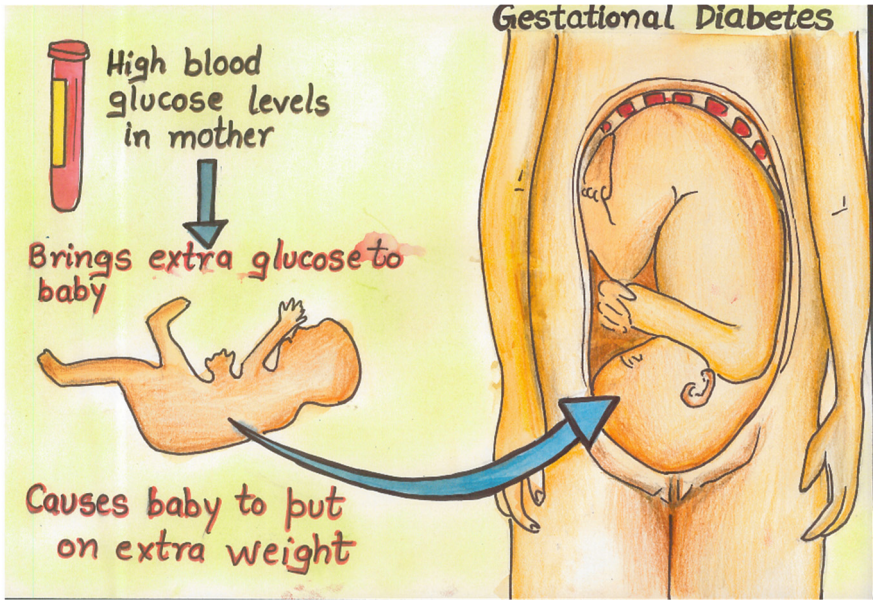



**Figure.3**
Overview of GDM. During pregnancy, hormonal changes can cause the body to be less sensitive to the effect of insulin. These changes can lead to high blood glucose levels affecting both mother and baby. (64)

*Hyperglycemia in the mother*

Insulin resistance in women with GDM is considered to be more severe and chronic as compared with the normal physiological insulin resistance seen during pregnancy, and most GDM women are, as mentioned above, likely to have had a higher degree of insulin resistance prior to pregnancy. Thus, insulin resistance in GDM may be considered as an exacerbation of pre-pregnancy insulin resistance as mediated by certain physiological changes including increased maternal adiposity as well as insulin desensitization effects of a range of placental hormones released during pregnancy (65). The hormones suspected to be causing insulin resistance in normal and GDM pregnancy includes human placental lactogen, human placental growth hormone, corticotropin-releasing hormone, prolactin, progesterone, and leptin (66).

The enhanced production of these pregnancy hormones results in increased insulin resistance at the post-receptor level in insulin sensitive tissues including muscle, liver and adipose tissue. At the intracellular and receptor level, the defect has been reported to include a decrease in the insulin receptor substrate 1 tyrosine phosphorylation as well as diminished phosphorylation of the intracellular portion of the insulin receptor (67). Together, this may result in impaired insulin action at the post-receptor level as shown in skeletal muscle biopsies (66,68-74).Studies of women with GDM have shown increased levels of pro-inflammatory markers and

cytokines including both TNFα, and IL-6, (75)as well as decreased levels of adiponectin, which is known to be an important insulin sensitizing hormone produced by adipose tissue (75). These, to some extent physiological metabolic derangements, are considered to further trigger and contribute to the development of exaggerated insulin resistance in pregnancies complicated with GDM (76). Other general factors like increased plasma free fatty acid levels as well as adipocyte size during pregnancy are suspected to contribute to the increased insulin resistance in GDM women (77).

*Hyperglycemia in the fetus*

As described above, the high maternal glucose levels are transferred to the fetus, causing fetal hyperglycemia. To bring the glucose levels down, the fetus responds with an increased insulin production. Insulin is a strong growth factor, and hyperinsulinemia in the fetus therefore leads to enhanced fetal growth (78)(fig.3). This subsequently leads to a high birth weight of the infant known as macrosomia and is associated with an increased risk of obstetric complications (79-82). Based upon the above mentioned physiological glucose and insulin changes in pregnancy, the "Pedersen hypothesis" postulates that maternal hyperglycemia and poor diabetes control, gives rise to fetal hyperglycemia and hyperinsulinemia, macrosomia, decreased oxygen availability as well as increased fetal adiposity (fig. 4) (83).

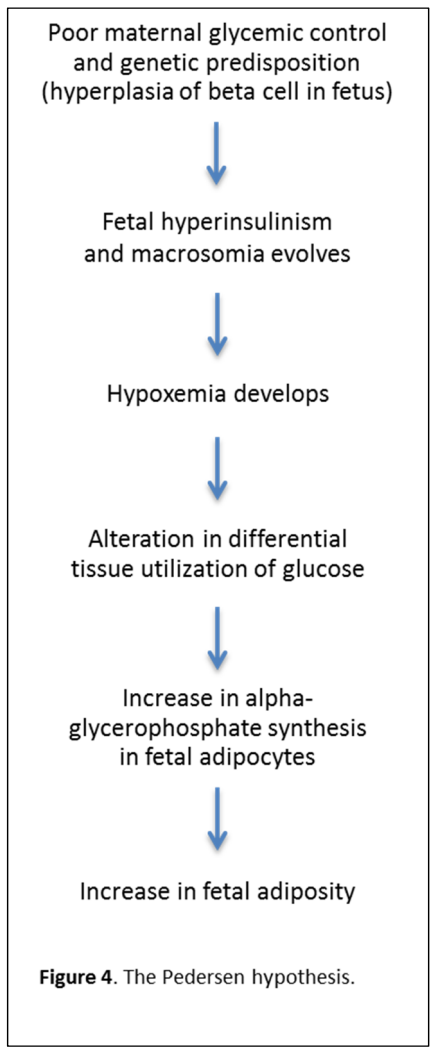



**Figure 4**. The Pedersen hypothesis.

Soon after pregnancy, most GDM women exhibit normal plasma glucose levels, but 30-50% of women with GDM will with time develop T2D (84). Indeed, GDM and T2D share a range of etiological genetic and non-genetic risk factors as well as pathophysiological features including both impaired insulin secretion and insulin resistance (85-88).

# GDM diagnosis

There are no uniform or generally used standardized consensus criteria for screening or diagnosis of GDM. Many controversies continue to exist in this field and various different screening procedures and diagnostic criteria have been used over time around the globe.

*GDM Screening*

Previously, the American Diabetes Association (ADA) recommended screening of high-risk population groups selectively. But over the years, studies have shown that compared to selective screening, universal screening for the diagnosis of GDM detected more cases and resulted in improved both maternal and neonatal prognosis (89).

Universal screening can be performed using random tests for plasma glucose levels or oral glucose tolerance tests (OGTT) (90). Women at high risk of developing GDM should undergo screening during first trimester and if not diagnosed with GDM then, the test should be repeated at 24-28 weeks of gestation (91). Women are considered at high risk for GDM if they are of high age, obese, multiparous, have a positive family history of diabetes or GDM, have poor obstetric history, chronic hypertension, multiple pregnancies and are of high-risk ethnicity (e.g. Hispanics, African, Asian, Native American) (92). Presently, universal screening of all pregnant women between gestational weeks 24-28 using a standardized 75g OGTT is recommended by the IADPSG (table 1) (93,94). In 2015, the use of the IADPSG diagnostic thresholds was accepted by the Swedish National Board of Health and Welfare and by the European Board and College of Obstetrics and Gynecology (94,95). In other parts of Europe, both EASD, WHO and IADPSG guidelines using a 75g OGTT are used (95,96, 103) (table 1). However, the American College of Obstetrics and Gynecology continues to use ADA criteria with a 2-step procedure (97).

*GDM criteria*

There have been different approaches to justify and validate different diagnostic criteria used by respective population groups. The proposed key parameters, such as perinatal mortality or morbidity, risk of development of subsequent diabetes in the mother, different statistical limits used for defining an abnormality and GDM in equivalence to diabetes outside pregnancy by applying similar diagnostic thresholds as used for overt diabetes, has formed the basis of the diagnostic definition of GDM. Adding to this confusion, there have been differences in OGTT procedures (amount of glucose and timing of measurements) used, as well as the type of sampling

(venous and capillary) performed for glucose measurements as shown in table 1, for defining these diagnostic criteria applied in different continents.

**Table 1:**
Diagnostic criteria for GDM (22,98-104).

| Criteria | Glucose (g) | FPG mmol/l (mg/dl) | 1-hour PG | 2-hour PG | 3-hour PG | Diagnosis (positive) |
|---|---|---|---|---|---|---|
| **WHO 1999** | 75 | 7.0 (126) | - | 7.8 (140 | - | ≥1 |
| **WHO 2013 (IADPSG)** | 75 | 5.1 (92) | 10.0 (180) | 8.5 (153) | - | ≥1 |
| **EASD** | 75 | 7.0 (126) | 11.0 (198) | 9.0 (172) | - | ≥1 |
| **ADA** | 75/100 | 5.3 (95) | 10.0 (180) | 8.6 (155) | 7.8 (140) | ≥2 |
| **ADIPS** | 75 | 5.5 (99) | - | 8.0 (144) | - | ≥1 |
| **Carpenter and Coustan** | 100 | 5.3 (95) | 10.0 (180) | 8.6 (155) | 7.8 (140) | ≥2 |
| **NDDG** | 100 | 5.9 (105) | 10.6 (190) | 9.2 (165) | 8.1 (145) | ≥2 |
| **O'Sullivan and Mahan*** | 100 | 5.0 (90) | 9.2 (165) | 8.1 (145) | 7.0 (125) | ≥2 |

Venous plasma values except * using venous whole blood. FPG: Fasting plasma glucose, PG: plasma glucose.

The World´s Health Organization (WHO) in 1999 came with modified 2 hr-75 g OGTT post load threshold value for diagnosis of GDM that predicted adverse maternal or fetal outcomes ( 105-107).The WHO criteria were in general considered those most easy to apply as well as feasible to use in clinical practice. Nevertheless, with the WHO1999 criteria it was unclear as to how much and which adverse outcomes were associated with the diagnosis of GDM per se, including which adverse outcomes that could have been explained by confounders like obesity, advanced maternal age, diet, socioeconomic conditions or other medical complications (108). Indeed, any such confounders may negatively impact the probability of improving the adverse outcomes of GDM with interventions targeting the elevated plasma glucose level in pregnancy, being the prime indicator and therefore treatment target of the disease. Pertaining to the above question, different studies mentioned various criteria used for GDM diagnosis and its implications (109,110).

Most of the criteria and diagnostic cut-off thresholds were previously based upon the risk of women developing T2D postpartum, and not directly on the pregnancy outcomes (98). The basis for the diagnosis of GDM was coined by O'Sullivan and Mahan in the 1960s (98), and was subsequently modified by Carpenter and Coustan (100). The most common diagnostic criteria used in United States are those recommended by American Diabetes Association (ADA) or the National Diabetes Data Group (NDDG) (99,101). The ADA supported the use of Carpenter-Coustan approach using 100g OGTT for 2hr glucose values.

In India, the DIPSI (Diabetes in Pregnancy Study group in India) criteria, which are modified from WHO 1999 criteria, are commonly used where a glucose

concentration of more than 140 mg 2hrs after a 75g glucose load, using a single prick, is considered GDM in most of States including Punjab, North India. Few have adopted the universal recommendation of IADPSG (WHO 2013) criteria in their respective regions. Guidelines and standardization of GDM diagnostic criteria yet needs introspection in nations like India where diabetes prevalence numbers are fast increasing. It also becomes imperative to determine whether prevalence and risk factors influencing GDM using the WHO criteria (FPG ≥7.0 mmol/l and/or 2-hr postprandial plasma glucose (PPG) ≥7.8 mmol/l) will be different from the proposed IADPSG criteria (FPG ≥5.1 and/or a PPG ≥8.5 mmol/l) and their implications in a given population.

*The HAPO Study*

The HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study addressed the question of how to define GDM based upon pregnancy outcomes in a comprehensive way (111). This was an international cohort of 23316 pregnant women from 9 different countries. These women were screened for GDM by performing 75g OGTT at 24-28 weeks of gestation (111), and the proposed diagnostic threshold was based on pregnancy outcomes with odds ratio of 1.75 for birth weight ≥$90^{th}$ percentile of the offspring, cord blood C-peptide ≥ the $90^{th}$ percentile, offspring percentage body fat ≥the $90^{th}$ percentile, primary caesarian section and neonatal hypoglycemia. The study reported a significant positive association between increasing glucose levels and secondary adverse outcomes, like premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyper-bilirubinemia, and preeclampsia. Notably, the reported continuous statistically significant relationship between maternal plasma glucose levels and adverse pregnancy outcomes r, did not define any obvious threshold, illustrating that even with these data in mind, any changes in GDM diagnostic criteria would still need to be somewhat arbitrary (111). The data nevertheless formed the basis for the IADPSG (International Association of Diabetes and Pregnancy Study Group) GDM criteria in 2010 characterized in particular by lower fasting plasma glucose cut off criteria compared with previous criteria (104,111,112). In 2013, the WHO subsequently adopted these criteria.

# GDM risk factors

Several factors influence a pregnant woman's risk of developing GDM, including previous history of GDM, obesity (BMI >30kg/$m^2$), increasing age, a past history of macrosomia, birth weight more than 4000g, family history of diabetes, multi-parity, history of Polycystic Ovarian Syndrome (PCOS) and a high risk ethnicity (97).

There is evidence of a 48% higher recurrence rate of GDM in multiparous women (113). Parity has been found to enhance the risk of GDM after 4$^{th}$ delivery even after adjusting for other co-founding factors. (114). Further, it was reported that increasing BMI lead to higher prevalence of GDM. An almost 4-fold increased risk of GDM was reported in obese women ( where obesity was defined as (greater than or equal to body mass index [BMI] 30 kg m2), severe obesity (BMI≥35 kg m and healthy weight between 18.5 and 24.9 kg m(115). The risk of developing GDM doubled in overweight women (116). Similar results were found in relation to age with increasing age being associated with increased the risk of developing GDM (117,118). Risk factors like PCOS (118,119) and family history of diabetes (120,121), considerably increased the risk of developing GDM in these women. Diabetes in first degree relative sis associated with increased risk of GDM using IADPSG criteria (121), with odds ratios of 1.6 to 3.0 (120). Ethnicity is also considered as an independent risk factor for GDM and subsequent T2D, and the prevalence of GDM is directly proportional to prevalence of T2D in a given ethnic group. (122-125). South Asian, Middle Eastern and Hispanics are among the ethnic groups with highest risk of GDM. These ethnic differences are attributed to differences in insulin secretion and action between populations (126-129), but the relative role of impaired insulin secretion or action, as well as the differential roles of genetics versus environmental factors are not known. Indeed, ethnic differences also exists within a population of a country, as for instance a South Indian study found a prevalence of GDM of 17.8% in urban, 13.8% in semi-urban and of 9.9% in rural areas (130), whereas the prevalence of GDM in North India has been unknown until recently.

# Maternal and fetal consequences of GDM

Hyperglycemia during gestation as already mentioned, contributes substantially to the risk of adverse fetal and maternal outcomes of a pregnancy. For the mother, there is increased incidence of macrosomia, caesarian section, shoulder dystocia, dyspraxia and hypertensive disorders (pre-eclampsia and gestational hypertension) among GDM pregnancies (131). In a review paper published in 2012 by Wendland et al, the risk of GDM defined using WHO1999 and WHO2013 criteria was reported. Risk ratios for complications compared with non-GDM pregnancies applying the above criteria were 2.2 and 1.4 for macrosomia, 1.4 and 1.2 for caesarian delivery and 1.7 (both criteria) for pre-eclampsia and large for gestational age (132). Furthermore, women with previous GDM have increased risk of cardiovascular disease (133,134), dyslipidemia, and subsequently of developing the metabolic syndrome after delivery (135,136). In a Danish study, an almost 3 times higher prevalence of the metabolic syndrome was reported in GDM women (137).

As mentioned earlier, GDM is also a risk factor for developing T2D later in life. In ethnic groups with history of high prevalence of T2D, the progression to develop diabetes following GDM is more rapid in comparison with others (138). It has been suggested that the incidence of T2D after GDM is up to 7-fold higher than after a normal pregnancy (139). (27,122,140-146). The cumulative incidence of T2D was 10% one year after GDM and increased further during the 5 years to 30% with a lifetime risk of about 50-70%(140). In another study by Kjos and Buchanan, a 17-63% risk of T2D was found 1-16 years after GDM (147). Lobner et al. showed 52.7% diabetes risk 8 years postpartum. (143). In a retrospective Danish study of diet treated GDM women, the incidence of diabetes doubled over the period of 10 years from 18.3% to 40.9% and was likely to be due to increase in BMI (148).

The offspring of a GDM mother have increased risk of complications during fetal life and development. As described previously, the Danish physician Jørgen Pedersen proposed in 1952 that intrauterine over-nutrient and subsequent excess fetal insulin production as a compensation to fetal hyperglycemia, contributes to the increased fetal growth (64,131). A high birth weight was associated with obstetrics complications both at the time of delivery as well as later in life (79-82 149). After delivery, there is an increased risk of hypoglycemia, (neonatal hypoglycemia) hyper-bilirubimenia, respiratory distress syndrome, polycythemia, hypocalcemia, hypertrophic cardiomyopathy (150). Fetuses exposed to maternal hyperglycemia are considered to have an abnormal intrauterine milieu for appropriate growth and metabolism. (122,123,135,151). Besides its immediate consequences for the infant and its mother during pregnancy and at birth, it predisposes the child to an increased risk of developing chronic diseases later in life (123-125) including hypertension, cardiovascular diseases and T2D (124,126152). It is though provoking that the major risk factors predicting these diseases later in life include both low and high birth weights defining a U-shaped relationship between birth weight and risk of these diseases later in life (153). Accordingly, the child of a GDM mother is at higher risk of developing obesity and T2D later in life as compared with offspring of a normal pregnancy (154,155). The prevalence of congenital abnormalities in infants born to GDM women needs to be more carefully examined in different populations(122).

In a study by Crowther et al., it was reported that treating hyperglycaemia in GDM women significantly reduced neonatal postpartum complications (156). Results by Langer et al. supported these results (82), and in a more recent study by Landon et al., even milder forms of GDM was associated with improved outcomes when treated with glucose lowering modalities (157).

# Heritability of GDM

Despite being a transitory type of diabetes, GDM has been shown to exhibit a high level of heritability (158), and it has been reported that its putative genetic dimension is associated with both the genetic makeup ofT1Dand T2D (159). Indeed, GDM women have in general a higher prevalence of a positive family history of diabetes as compared to normal glucose tolerant pregnant mothers 13.2% vs. 30% (160,161). Interestingly, it has been suggested that there is increased familial aggregation of diabetes on the maternal side in offspring with T1D whose mother had GDM (162). Simultaneously, there is evidence for clustering of T2D and IGT in families with GDM (163). To this end, a higher prevalence of T2D in mothers of women with GDM has been reported (164). Thus, GDM was reported to be 8 times higher among mothers of GDM women versus mothers of non-GDM s (164). Studies also suggested a higher prevalence of GDM in individuals whose parents have a positive family history of diabetes (163). Another study revealed that women with parental history of diabetes had a 2.3 fold higher risk of GDM when compared to those with non-diabetic parents (165). The estimated sibling risk ratio of GDM was found to be 1.75 (159,166), and it has been shown that women with a diabetic sibling have an 8.4 fold higher risk of GDM than women with no diabetic siblings (167). These studies together reveal a strong heritability and thus a putative genetic component in GDM. However, no studies have yet specifically assessed or measured inheritance of GDM by applying any form of twin study or familial clustering approach(159).

The human genome: The human genome comprises of approximately 3.1 million base pairs or nucleotides organized in chromosomes (168). Alleles are homologous copies of a gene. The discovery of the sequence of the human genome was first drafted and published in 2001(168,169). It has been shown that there are around 30,000 protein coding genes in a human genome (169-171). The Human genome is close to 99.9% identical between different individuals. The difference in nucleotide sequence between two unrelated individuals is the remaining 0.1% (172). A position where two, or in rare cases more than two, alternative bases are present in one nucleotide position of the human genome, is termed a Single Nucleotide Polymorphism (SNP) which are abundant in the human genome (173). ). The 1 000 genome project, showed approximately 38 million SNPs in the human genome, h 10 million of which have allele frequency of ≥0.1%. Thus, SNPs can be found at about y 300 base pairs (173-175). Depending on the location the SNP may or may not be functional. If a polymorphism is located within a coding region of a protein, it can either alter the amino acid sequence, called a non-synonymous SNP, or it does not change the amino acid sequence of the protein called a synonymous SNP (176). Most of these SNPs are present in the noncoding (noncoding SNPs). Even though synonymous SNPs do not affect the protein sequence, they can have functional

effects and by altering the expression of a gene or genes in the vicinity named expression quantitative traits (eQTLs).

Common SNPs can be associated with a disease and thus serve as a marker for the disease.

# Genetics of GDM and T2D

The pathophysiology of T2D involves an interplay between increased insulin resistance and decreased insulin secretion. Similarly, the hallmark of GDM is increased IR (insulin resistance) accompanied by decreased compensatory IS (insulin secretion) (58). Thus, both GDM and T2D share key pathophysiological features. To this end, both types of diabetes are influenced by risk factors like high BMI, age, ethnicity and not at least family history of diabetes, (177-182). Several studies of T2D have reported more than 100 SNPs associated with risk of T2D (183). Other studies have revealed genetic contributions to abnormal glucose e tolerance and GDM (184). Thus risk of GDM is likely to be increased by multiple genetic variants. However, the extent to which such genetic variants predispose the etiology of GDM needs to be determined. .

Studies on genetic risk loci for GDM are limited. Many studies have examined whether the same genetic risk variants, which increase risk of T2D, increase risk of GDM (185,186). In a study by Cho et al, 18 SNPs in nine T2D susceptibility loci were examined in Korean subjects to assess their association with GDM (185). And it revealed genetic variants in *CDKAL1* (CDK5 Regulatory Subunit Associated Protein 1 like 1) and *CDKN2A/2B* (Cyclin Dependent kinase Inhibitor 2a/2b) were strongly associated with risk of GDM and decreased insulin secretory capacity (185). Lauenborg et al also found that the *TCF7L2* (Transcription Factor 7-like2) variant showing the strongest association with T2D, and a variant in the *CDKAL1*gene were strongly associated with risk of GDM in European women (186). Another study by Kwak et al strong associations of variants in the *KCNQ1* (Potassium voltage-gated channel subfamily Q member 1), *CDKAL1* and *MTNR1B* (Melatonin Receptor 1 B) gene increased risk of GDM (187,188). Six genetic variants in five genes have been shown to impair beta-cell function; *CDKAL1, 1GF2BP2* (Insulin-like growth factor 2 mRNA binding protein 2) *KCNQ1, KCNJ11* (Potassium voltage-gated channel subfamily J member 11), *MTNRIB*, whereas variants in two common genes have been associated with insulin resistance *PPARG*; (peroxisome proliferator activated receptor – gamma) and *TCF7L2*. . Although, it has been studied that there is overexpression of *TCF7L2* gene in islets of T2D and

is associated with impaired insulin secretion, impaired incretin effect, and increase hepatic insulin resistance. Also a variant in the *GCK* (glucokinase) gene that regulates the threshold for glucose –stimulated insulin secretion in pancreatic islets and hepatic gluconeogenesis.has been associated with impaired insulin secretion (186,189-197)

In a meta-analysis, eight genetic polymorphism within or near the *TCF7L2, MTNRIB, 1GF2BP2, KCNJ11, CDKAL1, KCNQ1, GCK* genes were associated with risk of GDM (198). Studies in South Asian Indians revealed an association between the common *CDKAL1* variant and GDM (199). A study in Mexican women, showed an association between variants in the *TCF7L2, KCNQ1* identified association *CENTD2* (Ankyrin repeat and PH domain containing protein 1) and *MTNR1B* (rs1387153) genes with GDM (200).. Identification of genetic variants linked to GDM will contribute to better knowledge about the etiology of GDM

# Aim of this thesis

The overall aim of this thesis was to determine the prevalence of gestational diabetes, to assess pathophysiological aspects and to dissect the impact of genetic and non-genetic risk factors on susceptibility to GDM defined by WHO 1999 and WHO 2013 diagnostic criteria in North Indian women.

*The specific aims were:*

**Paper I**

To determine the prevalence of GDM comparing the previous WHO 1999 criteria to the WHO 2013 criteria and to examine the influence of various risk factors on both fasting and post prandial glucose concentrations in North Indian pregnant women.

**Paper II**

To determine the relative contribution of defects insulin secretion and insulin resistance to GDM defined by the WHO 1999 and adapted WHO 2013 and assess the possible influence of selected risk factors in North Indian pregnant women.

**Paper III**

To investigate whether common GDM and T2D loci from studies based on Indian and European populations associate with GDM in the Punjabi population and to further examine their role in North Indian GDM mothers.

**Paper IV**

To determine the phenotypic and genotypic differences in Indian and Swedish women with gestational diabetes.

# Study design and methodology

## Study design and participants

The current study was carried out in the North Indian state Punjab. A multistage random screening technique was applied for recruitment of pregnant women, and included selection of three major representative regions in Punjab (fig.5). There were nine recruitment sites including antenatal clinics from public, private and primary health care sectors as shown in table 2. The data were collected from August 2009 until December 2012.

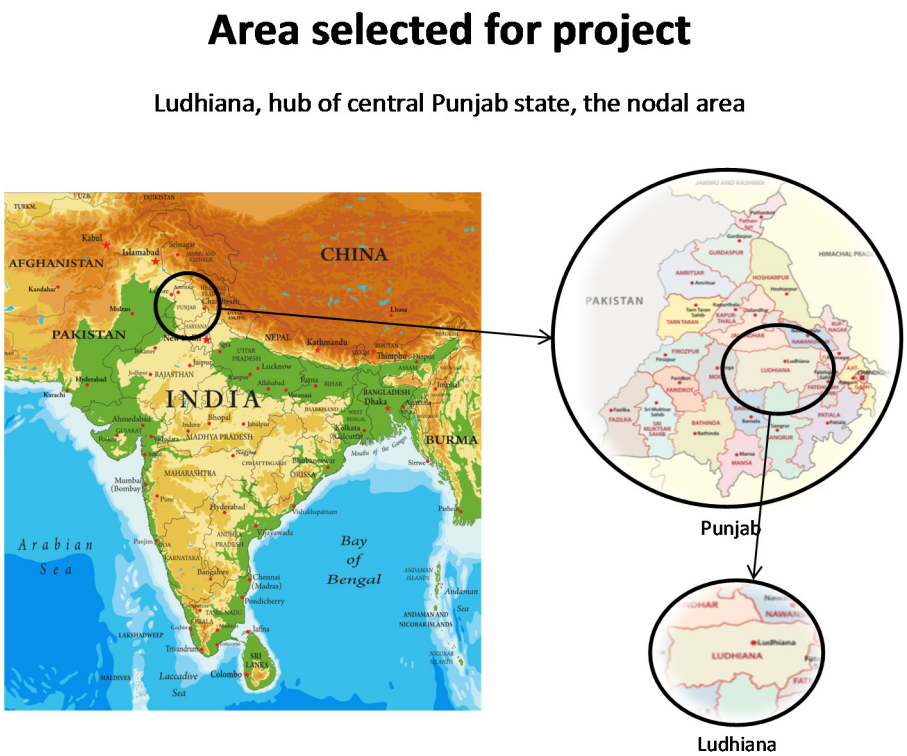



**Figure. 5**

**Table 2.**
The nine antenatal clinics included in the study.

| Category | Hospitals/PHCs |
|---|---|
| **Public Sector** | Govt. Medical College & Hospital, Patiala |
| | Govt. Medical College & Hospital, Amritsar |
| | Civil Hospital, Ludhiana |
| **Private Sector** | Deep Hospital, Ludhiana |
| | Shri Rama Charitable Hospital, Ludhiana |
| | Chawla Nursing Home (maternity home), Ludhiana |
| **Primary Health Centers** | PHC, Sahnewal, Ludhiana |
| | PHC, SidhwanKalan, Ludhiana and OR |
| | PHC, Machhiwara, Ludhiana |

At least 5000 pregnant women were aimed to be screened randomly for GDM. Women visiting the clinics belonged to diverse socio-economic backgrounds in both urban and rural settings. Since the selected hospitals were prominent medical care centers and commonly visited antenatal clinics by majority of population around the region, the subject participants formed the representative group of North Indian pregnant Punjabi women. The study included universal screening of all pregnant women visiting these antenatal clinics during gestational week 24-28 who were willing to participate. Women with pre-gestational diabetes were excluded from the study. The majority (70%) of women came in fasting, defined as overnight fast of 8-12 hours. Those who were not fasting were asked to come back the next day.

As shown in figure 6, at random 6255 women were invited to participate in the screening and of them, 1014 women declined participation. Consequently, 5241 women were screened for GDM, however due to inadequate data quality including missing data from questionnaires and/or blood samples, it was decided prior to the statistical analyses not to include results from 141 women resulting in 5100 participants. The main reason for declining participation was fear of being diagnosed with diabetes during pregnancy, which was considered a social stigma. The lack of time due to household routines (mainly urban), daily wagers and laborers (mainly rural) were expressed as reasons for not participating .The analysis was carried out on 5100 pregnant women samples drawn from these randomly selected women. All information material and consent forms were in three languages, Hindi (National), Punjabi (Regional) and English. Informed written consent was obtained according to the Indian Medical Research Council (ICMR) New Delhi guidelines, in the form of signature of a thumb impression (a proxy for illiterate subjects). The study was approved by the Regional Ethics Committee and the Directorate of Medical Research and Education of the State. In each of the selected study sites, a team of different healthcare professionals like nurses/mid

wives, parametrical staff and diabetic educators were assigned to inform and recruit eligible subjects. To ensure uniformity at all selected hospitals in performing screening and sampling, training sessions were conducted regularly.

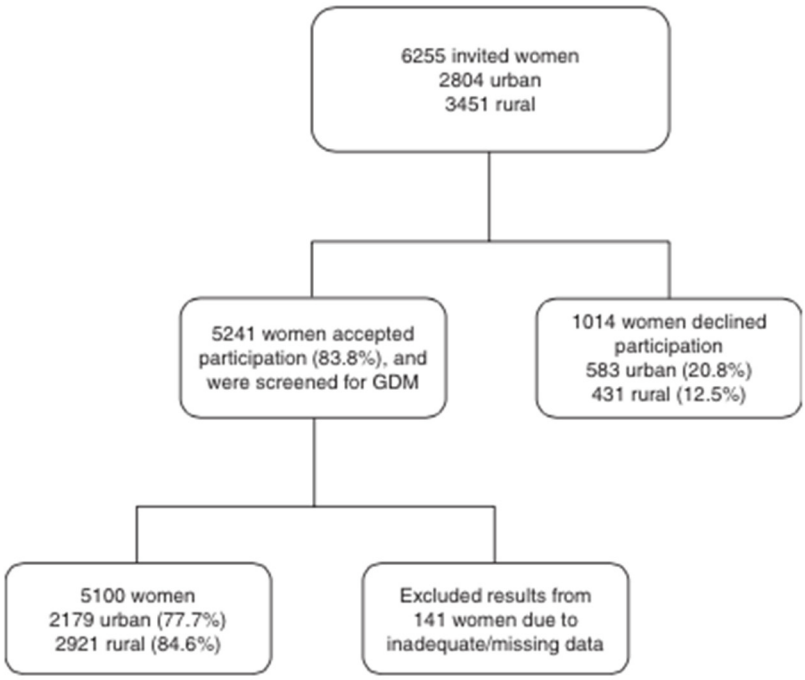



**Figure 6.**
Participation inclusion (201)

# Examinations and diagnosis

*Questionnaires*

The data were collected as a personal interview using a structured questionnaire. Information was filled in by a medical personnel for all women included in the study. Information about age, place of residence (rural/urban), education status (proxy for socio economic status - educated if able to provide a signature; illiterate if only able to give a thumb impression), religion, diet (vegetarian/non vegetarian), family history of diabetes (irrespective of type, in 1st and 2nd degree relatives), history of addictions, present and past obstetric history (complications if any) as

well as age at marriage was recorded. The height and weight were measured using standardized procedures and BMI was calculated.

*Oral glucose tolerance test (OGTT)*

A 2-hr OGTT was performed in all women. The OGTT procedures were standardized at all study sites, and the women were subjected to drink 75 g of glucose solution (250 ml) within five minutes. A fasting venous blood sample was drawn from an ante-cubital vein in 10 ml EDTA vacutainers (no fluoride). Fasting glucose concentration and fasting insulin measurements were determined from this venous sample. Based on enzymatic glucose oxidase method, calibrated glucometers were used. Validation of glucose values was performed in the lab using enzymatic reaction, glucose oxidase peroxidase (GOD-POD) method (Microlab 300, Merck Diagnostics, India) (201,202). Fasting plasma insulin concentrations were determined with ELISA using monoclonal antibodies (Insulin ELISA Kit, Diameter, Milan, Italy). The ELISA Kit had an intra Assay Variation (within run variation was determined by three different levels of serum in one assay) of <5.0% and inter Assay Variation (between run variation was determined by replicate measurements of three different level of serum indifferent lots) of <10.0%. The assay had an average accuracy of 96.9% I 5.4% (SD). The 2hr plasma glucose concentration was measured in capillary blood using Accu-Chek glucometer (Roche Diagnostics, Mumbai, India). This approach was used to keep the cost down and to make it feasible and convenient for the participant. At most of the sites, glucometer was used for both fasting and 2hr glucose concentration measures at a main laboratory and at bed-site sampling.

Two blood samples were drawn simultaneously 2 hours after the OGTT in 183 randomly selected women samples for comparative analyses of capillary plasma glucose (CPG) measured by glucometers with venous plasma glucose levels (VPG) measured in the laboratory by the GOD-POD method (203). The mean difference was 15%, with the CPG values being higher than VPG values which was in accordance with previous findings (204). Accordingly, the post OGTT CPG values were corrected (reduced) by 15%, and with the WHO criteria of GDM, the 2hr VPG cut-off level of 7.7 mmol/l was equal to a CPG level of 8.9 mmol/l measured by glucometers. We found a significant positive correlation between the CPG and VPG levels ($r=0.82$, $P<0.0001$).In one study by Balaji et al. in South Asian women, CPG was recommended as a feasible, economical and evidence based diagnostic tool for diagnosis of GDM in health care centers where laboratory technology was not available (205).

*Diagnosis of GDM*

As previously mentioned, there is consensus that the ideal time for testing the average-risk woman for GDM is between 24-28 weeks of pregnancy (91). Early

pregnancy is associated with increased insulin sensitivity, and fasting glucose values are thus lower during first and early second trimester in a normal pregnancy, compared to non-pregnant women. During the second trimester the degree of insulin resistance increase and glucose levels will rise if the woman cannot produce enough insulin to compensate for this resistance. However, it is recommended that GDM screening of high-risk pregnant women is performed early in pregnancy.

The GDM women included in the current study were screened during gestational weeks 24-28 and diagnosed using both the WHO 1999 and WHO 2013 criteria

According to the WHO 1999 criteria, GDM is defined as a fasting plasma glucose (FPG) level ≥7.0 mmol/l (126 mg/dl) or 2-h PG levels after a 75g OGTT ≥7.8 mmol/l (140 mg/dl)(table 1). WHO 2013 diagnostic criteria was based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel, that after reviewing the results of the HAPO and other studies which associated maternal glycaemia with perinatal and long-term outcomes in offspring, suggested to use different diagnostic threshold values in comparison with WHO1999 criteria. The WHO 2013 criteria proposed to lower FPG for diagnosis of GDM to ≥5.1 mmol/l (92 mg/dl) while a 2-hr PG threshold of ≥8.5 mmol/l(153 mg/dl) was proposed(90).

We applied adapted WHO 2013 criteria excluding the 1-hour glucose value to diagnose GDM. The current study did not include a 1-hr glucose sample since it was designed according to the DIPSI guidelines using 2-hr glucose value as diagnostic criteria. Furthermore, feasibility, compliance and cost had to be taken into account especially in rural settings in India.

*Homeostatic model assessment*

The homeostatic model assessment (*HOMA*) is a method used to quantify insulin resistance and beta-cell function in a steady state as percentages in normal reference population.(206).In 1976, Robert Turner and Rury Holman suggested that there existed a hepatic-beta cell feedback mechanism which determined fasting plasma insulin and glucose levels. The concept claimed that when there was a decreased insulin secretion, elevated fasting glucose levels depicted a compensatory state that maintained fasting insulin levels, further stating that the rise in fasting insulin levels was directly proportional to decreased insulin sensitivity (S). Based on this concept, a mathematical feedback model was developed (206). In 1985, David Matthews *et al* produced a computer model which was more structured and also available as a set of linear equations that gave an approximation of insulin secretory capacity (%B) and insulin resistance (reciprocal if % S) in a normal weight individual and

hypothetical 100% insulin secretory capacity, known as Homeostasis Assessment Model (HOMA)(207). In 1998, Jonathan Levy et al, came up with modified version of this model as HOMA 2 which is widely used as an application to determine beta cell capacity (HOMA-B) and insulin resistance (HOMA-IR) (208). Thus in the current study, measurements of fasting glucose and insulin concentrations was used to obtain surrogate measures of insulin action (HOMA2-IR) and insulin secretion (HOMA2-B) in the women with or without GDM defined by both WHO 1999 and WHO 2013 criteria using the HOMA2 calculator v2.2.3 http://www.dtu.ox.ac.uk/homacalculator/ (208).

# DNA Extraction

Genomic DNA was extracted from white blood cells (buffy coats) using a standard protocol. Briefly, the red blood cells were lysed leaving the white blood cells intact. These white cells are further lysed by specific white cell lysis solution containing proteinase K. Proteins were salt-precipitated and separated together with other debris in the cell with centrifugation. DNA was separated from the supernatant solution after clumping of debris (broken proteins, lipids, and RNA) occurred. DNA obtained was precipitated with 100% isopropanol, washed with 70% ethanol and hydrated with DNA hydration solution and stored at 20 °C (QIAGEN Autopure LS).

# Genotyping

The main method used for genotyping was the available Sequenom Mass Array Platform, San Diego, CA, USA.,2010 (Sequenom reagents, assays and protocols) PLEX using MALDI-TOF mass spectrometer (209). Individual were excluded with < 60% successfully genotypes SNPs as marker of bad DNA quality. SNPs were excluded when they had < 90% genotype success rate or when they deviated from Bonferroni-corrected Handy-Weinberg Equilibrium in each set of SNPs of the specific traits.

*Sequenom:*

*Locus Specific PCR Reaction:* A template PCR was carried out to amplify the region of interest. After adding PCR mix (DNA template, nucleotides- dDNTPs, catalyst enzyme-Taq DNA Polymerase, Primer Pairs, co-factor MgCl2, PCR buffer), the process was continued with denaturation (94 °C for 5 min), then repeated 30 cycles of denaturation (94-96 °C for 30s), annealing (30s), extension (72 °C for 30-60s),

final extension run at (72 °C for 10 min) and amplification was carried out to obtain an amplified PCR product. PCR product cleanup was performed. This TypePLEX reaction involved obtained amplified product to be treated with SAP (Shrimp Alkaline Phosphate). This neutralized unused dNTPs during initial amplification reaction. SAP cleaves a phosphate from unincorporated dNTPs converting them into dNDPs and rendering them unavailable for future reaction (fig.7).

*Locus-specific Primer Extension Reaction (IPLEX Assay)*: TypePLEX reaction cocktail (primer, enzyme, buffer, ddNTPs mass-modified terminal nucleotides) was added to the obtained products (209,210). In this primer extension reaction, an oligonucleotide primer anneals immediately upstream of the polymorphic site being genotyped. The primer and amplified PCR product is subjected to enzymatic addition of terminator nucleotides into the diagnostic site. It is done using programmed thermo cycling process. In the reaction mixture, all four terminator nucleotides A, T, C and G are present. The primer is extended by one of the nucleotides, which terminated the extension of the primer. Thus, the primer extension occurred depending upon the sequence of the variant site (allele), and is a single complementary mass-modified base (209,210). Mixing of different locus-specific primers, many individual loci of DNA with their corresponding SNP sites could be studied in one well reaction. Further, Sequenom spectro clean was performed. Here, the product was cleaned with cationic resin, which is pre-treated with acid reagent that removed Na+, K+, and Mg2+ ions.

*Spectro Chip Array spotting of Primer extension products:* A small volume (~25 nl) of analyte product obtained after clean-up was arrayed on existing matrix spots on the silica chip (Spectro Chip) by Mass Array nano dispenser.

*Primer Extension Products by Mass Spectrometry (mass ARRAY compact mass spectrometer):* With the use of MALDI-TOF (matrix-assisted laser desorption ionization-time-of-flight) mass spectrometry, the mass of the extended primer was determined. These primer masses present at the polymorphic site being studied represented a particular sequence or the alleles. Here, the chip was placed into the mass spectrometer and each spot was shot with a laser under vacuum by the (MALDI-TOF) method (211). It is believed that here, the sample molecules are vaporized, ionized, transferred electrostatically into a time-of-flight mass spectrometer (TOF-MS), there separated from the matrix ions, and are individually detected based on their mass-to-charge ratios, and analyzed. (211,212). Further, the results were obtained by automatic translation of the mass of the observed primers into a specific genotype for every sample or a reaction. This is done by Sequenom Spectro Typer, a software supplied by Sequenom (Spectro Typer) (fig.7).

*Taqman:* Genotyping of some SNPs was carried using Taqman allele discrimination assay. The assay was performed using an ABI Prism 7900 sequence detection

system (Applied Biosystems, Foster city, CA, USA) according to protocols. Primers and probes were designed using Assays-by-Design (Applied Biosystem,2015). Figure output from software which was used to analyze genotyping data (213). Taqman allelic discrimination was used to genotype SNPs separately which did not have a successful run and analysis results on Sequenom. Each assay detected specific SNP allele in an individual. It was performed using florescent labeled probes. These specific probes discriminated between alleles (214). To differentiate between two alleles, two different colors of dye are used with which they are labeled. There is a quencher preventing the fluorescence from the dye when the probe is intact.

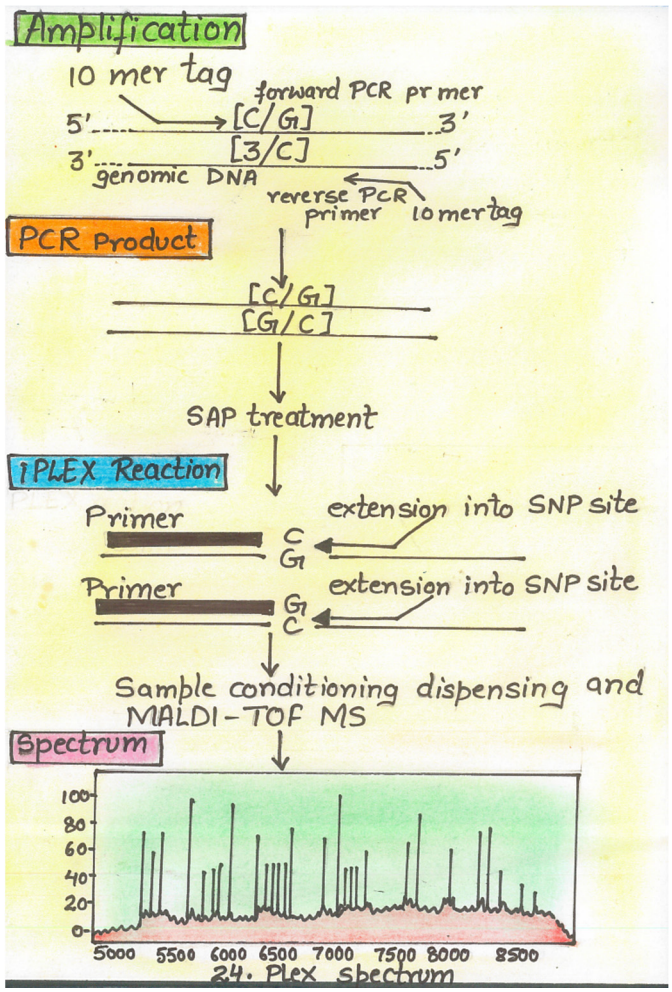



**Figure 7.**
'Sequenom' Flow chart

The principle followed here is that with the help of Taq DNA Polymerase enzyme's exo-nuclease activity, the hybridized probes with the same sequence attached, are cleaved. This results in the separation of the reporter dye from the quencher allowing the fluorescence to be emitted (homozygous carriers of an allele emit same color and heterozygous carriers having both signals from two dyes emit two colors). Only the cleaved probe emitted the signal. This allowed for a specific discrimination between the two colors representing two different alleles. Allele discrimination was performed on the ABI 7900HT sequence detection system (Applied Biosystems, Foster City, CA) (215)(fig.8).

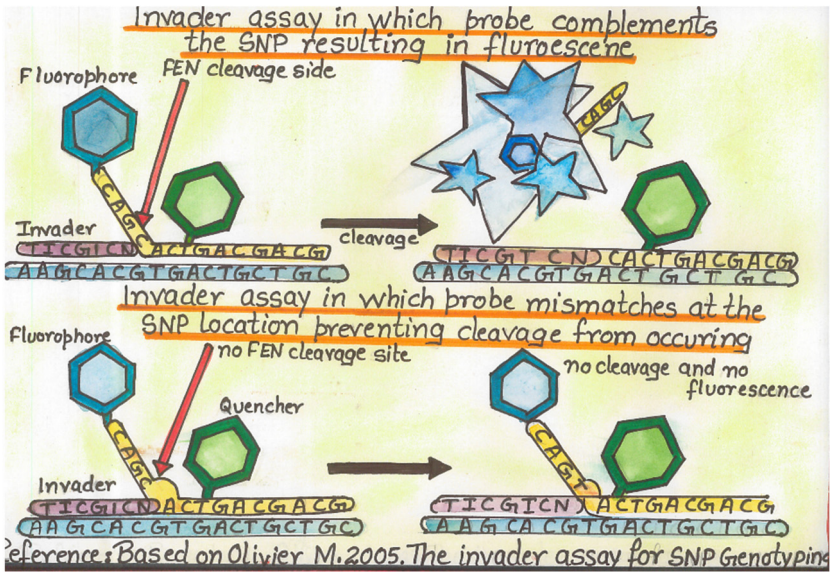



**Figure 8.**
'Taqman' probes and cleavage

In total, genotyping data was obtained for 4018 women. The study characteristics are noted below (table 3).

**Table 3.**
Characteristics of study participants.

| | N | Mean | SD |
|---|---|---|---|
| **Age (years)** | 4018 | 21.41 | 3.40 |
| **BMI (kg/m$^2$)** | 4018 | 24.11 | 4.34 |
| **Fasting plasma glucose (mmol/l)** | 4018 | 4.81 | 0.76 |
| **Plasma insulin (pmol)** | 4018 | 54.25 | 61.86 |
| **2 hour glucose (venous, mmol/l)** | 4018 | 6.20 | 1.37 |
| **HOMA2-B** | 3680 | 104 | 55.71 |
| **HOMA2-IR** | 3680 | 0.97 | 0.74 |

# Statistics

*Paper I*

Based on different criteria and cut-off thresholds used to diagnose GDM in the study (WHO 1999 and WHO2013 criteria), separate statistical analysis was done to obtain prevalence of GDM and various risk factors influencing GDM. Group means of FPG and 2-h PG levels and group means of non-GDM and GDM women were determined by ANOVA (Analysis of Variance). A linear regression analysis was the statistical method used to determine the relation between fasting glucose and 2-hour prandial glucose levels and risk variates influencing both glucose values. The relationship between GDM and different environmental risk factors selected in the study was tested. This was done by using multivariate logistic regression analysis with backward elimination of independent variables. The Pearson ($c^2$ test) test was used for comparison of group frequencies. Two-sided P-values of $\leq 0.05$ were considered statistically significant. All the statistical analyses in the study were performed using Stata 13 (Stata Corp, College Station, TX, USA).

*Paper II*

The statistical interpretation of data was performed using Student's t-tests for comparing different mean values obtained between GDM and Non-GDM subjects, using A Z-Test when comparison was to be made within and between the groups and further using analysis of variance (ANOVA) test for multiple comparisons between variables. In addition, the influence of different demographic risk factors, BMI, age, family history, habitat (urban vs. rural), diet (vegetarian vs non-vegetarian), religion and education (literate vs illiterate) on metabolic parameters HOMA-IR and HOMA-B was evaluated. For this, a linear regression analysis, adjusted for independent variables was used. These various statistical analyses applied in the study were performed using SPSS software v. 20.0 (IBM, NY, USA). A two sided p-value of $\leq 0.05$ was considered statistically significant.

*Paper III*

A logistic regression equation was used to assess the association of SNPs with GDM risk which was adjusted for BMI and age of the mother. The results were tabulated as ORs and their corresponding 95% confidence intervals (CI). Further, taking maternal age and BMI as covariates, a linear regression analysis was run to

determine the association of previously studied glycemic traits loci (FBS, PPBS, HOMA2-B, HOMA2-IR) were with their corresponding traits. Normalization of data was done with logarithmic transformation in all analysis for skewed distribution. A p-value of ≤0.05 was considered significant statistically in all analysis. The power to determine GDM 2013 associations for 79 SNPs with Bonferroni corrected significance level of 0.0006, allele frequency of 0.3 and effect 1.3 was 0.97, and for effect 1.2, was 0.64 for the same frequency. In GDM1999 associations, it was 0.39 and 0.12 respectively. In addition, the power assessed for association with quantitative traits was 1 at alpha 0.05 for effect allele frequency of 0.3 (216,217). Genetic risk scores were evaluated on commonly studied loci associated with insulin secretion and insulin resistance for insulin secretion and insulin resistance respectively. In order to assess if different interpretations of criteria altered genetic associations, logistic regression analysis adjusting for BMI and age was performed with the GDM as outcome where GDM was defined as (i) FG ≥ 7.0, (ii) 2 hr glucose ≥ 7.8, (iii) FG ≥ 5.1, (iv) 2hrG ≥ 8.5 (v) FG 7.0 and 2hr glucose 7.8 and (vi) FG ≥ 5.1 AND 2hr glucose ≥ 8.5. STATA was used for all calculations in this analysis.

*Paper IV*

GDM here was defined using Swedish criteria due to availability of phenotypes in the Swedish cohort. Chi-square test was used to compare allele and genotype frequencies between groups. The difference in the group means and their significance was tested by Mann-Whitney U-test or analysis of variance (ANCOVA) with BMI and age as covariates. Normalization of data with skewed distribution was obtained by inverse normal transformation. Association of selected SNPs with GDM was assessed by logistic regression analysis adjusted for maternal age and results presented as ORs with their 95% confidence intervals (CI) in plink (Plink v1.09). Linear regression analysis was done to test association of alleles with glucose, insulin and HOMA2-B and HOMA2-IR, adjusted for age. Power to detect association with GDM (Indian: 125 cases and 3893 controls) for 79 markers at a significance level of 0.05 was 0.04 under the additive model and 0.12 under the multiplicative model at 0.50 MAF and OR of 1.5. For the Swedish population group, with at 245 cases and 335 controls, the above figures were 0.06 and 0.17 respectively. Two-sided *p*-values of less than 0.05 were taken as statistically significant. For polygenic risk scores (PRS), PRsice was use for calculations (218). Genetic risk scores (GRR) for insulin secretion and action were formulated using PLINK (219). Here, we used 12 SNPs previously associated with insulin secretion and five SNPs with insulin resistance to build GRR for this study.

# Results

## Paper I

*Prevalence and Risk Factors of Gestational Diabetes in Punjab, North India – Results from a Population Screening Program.*

The WHO changed the diagnostic criteria for GDM in 2013 based on results from the HAPO study which found a continuous increase of adverse perinatal outcomes across the glucose concentration range (94). The new diagnostic criteria for GDM included fasting and 2-h blood glucose values with thresholds of ≥5.1 mmol/L and ≥8.5 mmol/L. The purpose of widening the diagnostic window was to improve both short- and long-term outcome for mother and offspring.

In the present study, we aimed to determine the prevalence and risk factors of GDM comparing the previous WHO 1999 criteria to adapted WHO 2013 diagnostic criteria (excluding 1-hr glucose values) in women in Punjab, North Indian. Five thousand one hundred (5100) pregnant women were recruited from nine different health care centers (public, private, rural and urban). The women were interviewed by study personnel using a questionnaire asking about residence, education, religion, diet, diabetes in the family, obstetric history, age when married etc. Gestational week was calculated and height and weight measured. The Women were subjected to a standardized 75-g OGTT where fasting and 2-hr blood samples were obtained (201).

We found that the prevalence of GDM in North Indian women was 9.9% using the previous WHO 1999 diagnostic criteria while it increased 3-fold to 34.9% applying the current WHO 2013 criteria.

The GDM women had significantly higher fasting and 2-h plasma glucose (FPG and 2-h PG) levels as compared to non-GDM women using both criteria ($p<0.001$). The non-GDM women had significantly higher fasting ($p<0.0001$) and 2-h ($p=0.004$) plasma glucose levels, whereas it was only the 2-h plasma glucose ($p<0.0001$) levels that were significantly increased in the GDM women when applying the WHO 1999 compared to the WHO 2013 criteria. The GDM women diagnosed according to the WHO 2013 criteria had higher BMI ($p=0.01$), were older ($p<0.001$) and shorter($p=0.01$)compared to non-GDM women. Applying the WHO 1999 criteria the GDM women were shorter than non-GDM women ($p<0.001$).

The relationship between FPG and 2-h PG levels for the 5100 women included in the study (fig.9) is not straight forward or linear, in that different women are

diagnosed with GDM using the different criteria; 7.2% had GDM by criteria, 1.8% by WHO 1999 criteria and 27.7% by WHO 2013 criteria only. The remaining 63.3% of women were classified as non-GDM by both criteria.

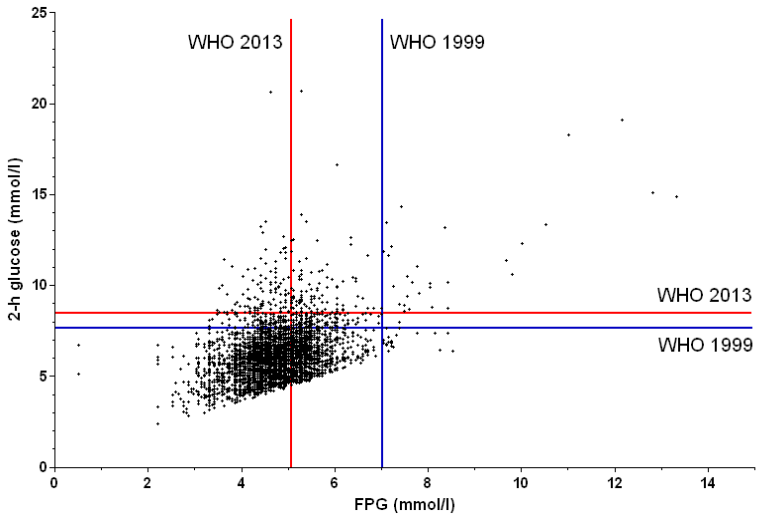



**Figure 9.**
WHO 2013 cut off is shown in red and WHO1999in blue.

With regards to risk factors, we found that urban life($p<0.001$), Sikh religion($p=0.04$ and $p<0.001$), vegetarianism (FPG $p=0.004$), increasing age($p<0.001$) and BMI($p<0.001$), family history of diabetes($p<0.001$)were associated with significantly increased FPG and 2-h PG levels. Illiteracy was only associated with increased 2-h PG level ($p=0.05$). As for the two different criteria, WHO 2013 criteria were urban life($p<0.001$), vegetarianism($p=0.04$), and increasing age ($p=0.004$)associated with a significant increased prevalence of GDM whereas urban life($p=0.001$), Hinduism($p=0.02$), non-vegetarian lifestyle($p=0.001$) and illiteracy ($p<0.001$)were associated with a significant increased GDM prevalence.

Using a logistic regression analysis, we found that the independent risk factors for GDM using WHO 1999 were urban life ($p=0.001$), Hindu religion($p<0.001$), illiteracy($p<0.001$), non-vegetarian lifestyle($p<0.001$), low height ($p<0.001$)and increasing BMI($p=0.02$). Independent risk factors for GDM using WHO 2013 criteria were urban life($p<0.001$), increasing age($p=0.001$) and a low height($p=0.005$). Finally, the independent risk factors possibly influencing FPG were urban life($p<0.001$), family history of diabetes($p=0.003$), illiteracy($p=0.007$), age ($p<0.001$)and BMI ($p<0.001$) and factors influencing 2-hr PG were urban life($p<0.001$), height($p<0.001$), illiteracy($p<0.001$), BMI ($p<0.001$)and a family history of diabetes($p<0.001$).

# Paper II

*Insulin Secretion and Action in North Indian Women during Pregnancy.*

Lowering the fasting glucose cut-off level from 7.0 to 5.1 mmol/L according to the new WHO 2013 criteria resulted in a 3-fold increase in GDM in North Indian women. The plasma glucose threshold for GDM is currently controversial, and potential differences in underlying pathophysiological mechanisms characterizing women diagnosed with WHO1999 and WHO2013 are unknown.

Here we aimed to determine the impact of defects in insulin secretion and action on development of GDM diagnosed by WHO 1999(GDM1999) and adapted WHO 2013 (GDM2013) criteria in 5100 North Indian pregnant women (218). A 75-g standardized OGTT was performed and beta-cell function (HOMA2-B) and insulin resistance (HOMA2-IR) were determined by the HOMA2 calculator (203). Both the WHO1999 (FPG ≥7.0 and/or 2-hr PG≥7.8 mmol/L) and the adapted WHO 2013 (FPG ≥5.1 and/or 2-hr PG ≥8.5 mmol/L) criteria were used to diagnose GDM (202).

An OGTT was performed in 4665 women out of the 5100 pregnant women (91.5%). Using the adapted WHO 2013 criteria, we found that the GDM women had significantly higher age than pregnant women with normal glucose tolerance women ($p \leq 0.001$). Furthermore, GDM women had lower height compared with normal glucose tolerance women ($p=0.001$ and $p=0.008$) also diagnosed by both criteria. The fasting glucose levels were significantly higher in women diagnosed according to the GDM2013 compared to GDM1999 criteria ($p \leq 0.001$), whereas we found the contrary for the 2-hour glucose levels ($p=0.001$). The GDM women had significantly lower insulin secretion (HOMA2-B) as compared to the normal glucose tolerance women diagnosed by both criteria (all $p \leq 0.001$). The degree of insulin resistance (HOMA2-IR) was significantly higher in women with GDM versus women with normal glucose tolerance using the adapted GDM2013 criteria ($p \leq 0.001$, adjusted $p=0.008$).

Of the factors influencing insulin secretion we found that urban life($p \leq 0.001$), Hindu religion($p \leq 0.001$), low BMI ($p \leq 0.001$) and illiteracy ($p=0.002$)were associated with lower HOMA2-B. HOMA2-IR was significantly increased by rural life ($p=0.01$), Sikh religion ($p \leq 0.001$), increasing age and BMI ($p \leq 0.001$), family history of diabetes ($p \leq 0.001$) and literacy ($p=0.002$).

# Paper III

*Association of Genetic Risk Variants and Glucose Intolerance during Pregnancy in North Indian Population.*

In previous reports it has been shown that GDM and T2D share common genetic background. In this study, we aimed to explore if common and known T2D risk variants associated with GDM in North Indian pregnant women diagnosed with various interpretations of existing criteria. We obtained genotyping data for 4018 pregnant women. The study characteristics obtained are shown in table 4.

Applying the WHO 2013 criteria resulted in a total of 1386 women with GDM (34.5 %) whereas the number was 346 (8.6%) when WHO 1999 criteria were used. Notably, only 283 (7.0%) women were diagnosed using both GDM 2013 and GDM 1999 criteria (fig. 10). A total of 1386 (34.5%) women were diagnosed as GDM defined by WHO 2013 criteria whereas 346 (8.6%) were diagnosed GDMs when WHO1999 criteria was applied and only 283 (7.0%) women were diagnosed using both GDM 2013 and GDM 1999 criteria (fig. 10) in this North Indian pregnant group population. Insulin secretion (HOMA2-B) was lower in GDM mothers defined by both criteria (WHO1999 and WHO2013) in comparison with normal glucose tolerant women and also was lower in T2D individuals compared to GDM (fig. 11). HOMA-IR was found to be higher in GDM mothers than euglycemic mothers but also was lower than insulin resistance in women with T2D(fig. 12).

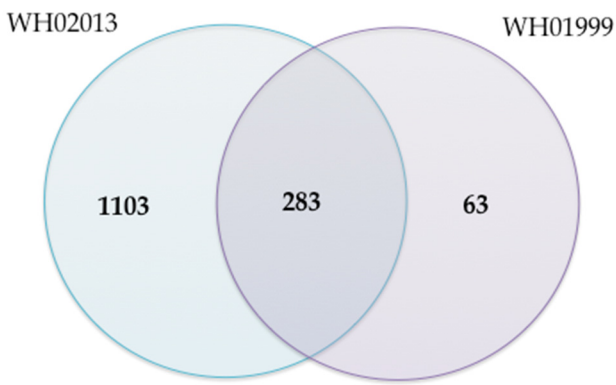



**Figure 10.**
Number of GDM women according to WHO2013 and WHO1999 criteria

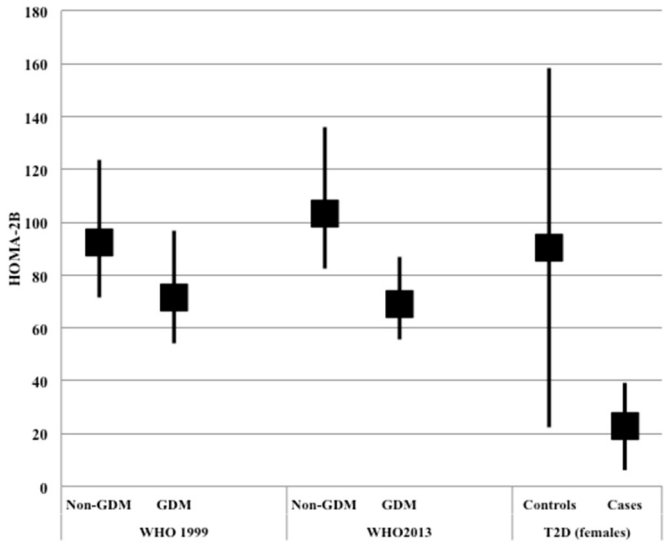



**Figure. 11.**
Insulin secretion (HOMA-B) in GDM, T2D, normal glucose tolerant non pregnant women and healthy pregnant Punjabi women. T2D and data calculated from Been et al, Nutr Metab Cardiovasc Dis. 2013.

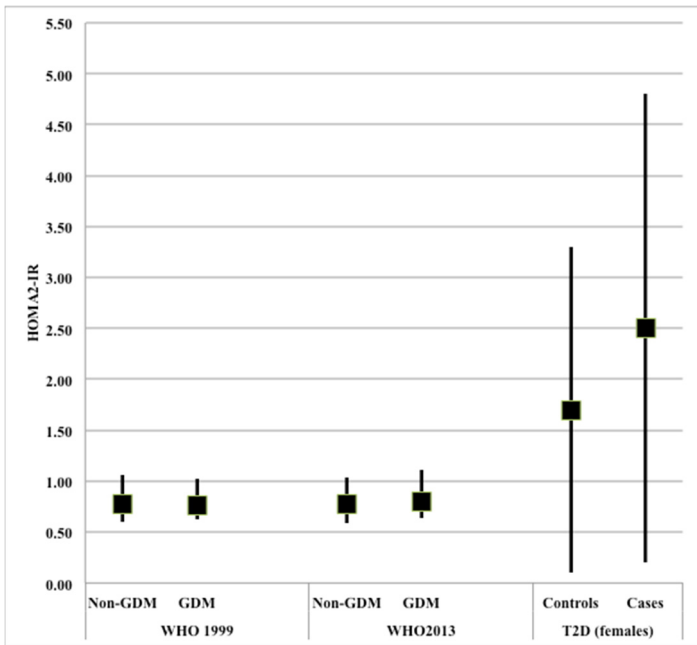



**Figure. 12.**
Insulin resistance (HOMA-IR) in GDM, T2D, non-pregnant normal glucose tolerant and pregnant Punjabi women with NGT. T2D and data calculated from Been et al, Nutr Metab Cardiovasc Dis. 2013.

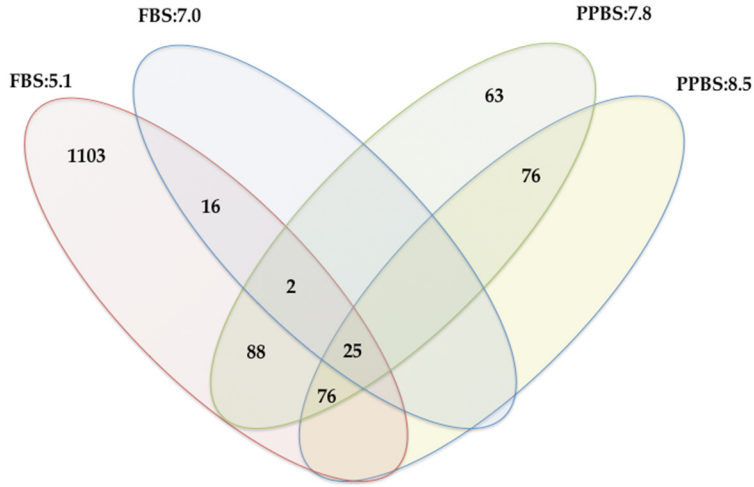



**Figure. 13.**
Distribution of GDM according to different interpretations of WHO1999 and WHO2013.

**Table 4.**
Study population characteristics

| **Subject characteristics** | | | |
|---|---|---|---|
| | N | Mean | Stddev |
| Age (years) | 4018 | 21.41 | 3.40 |
| BMI | 4018 | 24.11 | 4.34 |
| Fasting plasma glucose (mmol/l) | 4018 | 4.812 | 0.76 |
| plasma insulin (pmol) | 4018 | 54.25 | 61.86 |
| 2 hour glucose (venous, mmol/l) | 4018 | 6.20 | 1.37 |
| homa2_b with acceptable steady state glucose and insulin values | 3680 | 104.02 | 55.71 |
| homa2_ir with acceptable steady state glucose and insulin values | 3680 | 0.97 | 0.74 |

## Associations with previously studied SNPs:

Six SNPs previously associated with GDM or T2D in India (199, 220-223) (supplementary table 1) and 79 SNPs previously associated with T2D risk in Europe and elsewhere (some of these also with GDM risk) in GWAS studies upto 2012 were selected for the present study (Supplementary table 1) (224). No association between 6 selected SNPs previously associated with either GDM or T2D and in Indian populations and women here defined as GDM using either WHO1999 or WHO2013 criteria was seen. (table 5, supplementary table 5). Out of the 12 selected previously studied GDM risk loci, the T allele of the missense SNP rs5219 in the *KCNJ11* gene was nominally associated with GDM1999 (p= 0.019)(table 6). When assessed for their association with 12 selected GDM risk loci previously studied, the

T allele of SNP rs5219 in the *KCNJ11* gene was found to be nominally associated with GDM1999 (p= 0.019)(table 6). Paradoxically, the risk allele A of SNP rs11708067 in the *ADCY5* gene here revealed decreased risk in GDM2013 (p=0.037) (table 6) but not in GDM1999 women. The SNP rs2796441 in the *TLE1* gene was associated with decreased insulin secretion (p=0.013) (Supplementary table 2).

Among previously reported T2D genetic risk variants, T2D risk allele C of SNP rs13389219 in *GRB14* was associated with GDM1999 (p=0.022) (table 7) and nominally associated with GDM2013 (p=0.058, table 4) . SNP rs11920090 of *SLC2A2* associated with GDM2013 (p=0.030) (table 7) and also with GDM while applying diagnostic cut off threshold as 2-hour glucose ≥8.5, (p=0.032), FBS ≥5.1 (p=0.053), FBS ≥5.1 and 2-hour glucose ≥8.5 both (p=0.050) (supplementary table 5).

Paradoxically, T2D risk allele A in SNP rs11605924 of *CRY2* associated with decreased risk of GDM1999 (p=0.025) (table 7). Interestingly, it associated with GDM defined using diagnostic cut off value for GDM as 2-hour glucose ≥ 7.8 (p=0.024) (supplementary table 5) and also as 2-hour glucose ≥ 8.5, (p=0.028) (supplementary table 5). The same SNP also associated with decreased 2-hour glucose in GDM2013 women (p=0.038) (supplementary table 4). Similarly, T2D risk allele A of SNP rs1552224 of *CENTD2* associated with reduced risk in GDM2013 women (p=0.001) (table 6) and with GDM defined with FBS cut-off of ≥ 5.1 (p=0.007) (supplementary table 5) in this cohort. In addition, we found that T2D risk allele A in rs11071657 at the *FAM148B* genetic loci associated with increased insulin secretion (p=0.044) (table 8) when looked for association between HOMA-B in these women and 12 SNPs previously associated with insulin secretion. When assessed for insulin resistance, among 6 SNPs previously associated with insulin resistance, 3 SNPs here associated with HOMA2-IR (table 9). The C allele of rs7607980 in the *COBLL1* gene associated with decreased HOMA2-IR (p = 0,0001), C allele of rs13389219 near *GRB14* (p = 0,026) and A allele of rs10423928 in the intron of the *GIPR* gene (p = 0.012) associated with increased HOMA2-IR (table 9).

**Table 5:**
Association of previously reported GDM and T2D loci from Indian population based studies with risk of GDM according to both criteria

| Genotype | EA | Chr | Gene/nearest gene | Location | OR_WHO1999 | lower CI | upper CI | p_who1999 | OR_WHO2013 | lower CI | upper CI | p_who2013 | n |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs998451_A | A | 2 | *TMEM163* | intron | 0,987 | 0,795 | 1,224 | 0,902 | 0,959 | 0,843 | 1,090 | 0,518 | 3882 |
| rs1799999_A | A | 7 | *PPP1R3A* | missense | 0,862 | 0,728 | 1,020 | 0,083 | 0,997 | 0,905 | 1,098 | 0,953 | 3890 |
| rs689_A | A | 11 | *INS* | 5'UTR | 1,077 | 0,879 | 1,319 | 0,474 | 1,033 | 0,914 | 1,167 | 0,603 | 3903 |
| rs9552911_A | A | 13 | *SGCG* | intron | 1,057 | 0,830 | 1,347 | 0,653 | 1,017 | 0,875 | 1,183 | 0,824 | 3890 |
| rs4812829_A | A | 20 | *HNF4A* | intron | 1,040 | 0,871 | 1,240 | 0,667 | 0,988 | 0,890 | 1,096 | 0,814 | 3801 |
| rs7178572_G | G | 15 | *HMG20A* | intron | 0,988 | 0,832 | 1,173 | 0,891 | 1,017 | 0,921 | 1,122 | 0,743 | 3541 |

**Table 6:**
Association of previously reported GDM loci with risk of GDM according to both criteria

| | | | | | WHO 1999 | | | | WHO 2013 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | EA | Chr | Gene/nearest gene | Location | OR | CI(lower) | CI(upper) | p-value | OR | CI(lower) | CI(upper) | p-value | N |
| rs9939609_A | A | 16 | *FTO* | Intron | 1,042 | 0,860 | 1,262 | 0,676 | 0,988 | 0,884 | 1,105 | 0,834 | 3120 |
| rs2796441_G | G | 9 | *TLE1* | Intergenic | 0,993 | 0,843 | 1,169 | 0,929 | 1,072 | 0,975 | 1,179 | 0,152 | 3905 |
| rs560887_C | C | 2 | *G6PC2/ABCB11* | Intron | 1,182 | 0,920 | 1,520 | 0,191 | 1,114 | 0,967 | 1,284 | 0,134 | 3910 |
| rs11708067_A | A | 3 | *ADCY5* | Intron | 0,983 | 0,814 | 1,188 | 0,860 | 0,888 | 0,794 | 0,993 | **0,037** | 3877 |
| rs7754840_C | C | 6 | *CDKAL1* | Intron | 0,878 | 0,727 | 1,061 | 0,179 | 0,966 | 0,869 | 1,073 | 0,518 | 3721 |
| rs1111875_C | C | 10 | *HHEX* | Intergenic | 0,905 | 0,771 | 1,064 | 0,226 | 1,058 | 0,962 | 1,162 | 0,246 | 3901 |
| rs7756992_G | G | 6 | *CDKAL1* | Intron | 0,913 | 0,757 | 1,101 | 0,340 | 0,975 | 0,876 | 1,085 | 0,645 | 3686 |
| rs10811661_T | T | 9 | *CDKN2A/2B* | Intergenic | 0,990 | 0,776 | 1,263 | 0,936 | 1,088 | 0,947 | 1,251 | 0,233 | 3890 |
| rs4402960_T | T | 3 | *IGF2BP2* | Intron | 1,024 | 0,871 | 1,204 | 0,772 | 0,950 | 0,864 | 1,045 | 0,293 | 3750 |
| rs13266634_C | C | 8 | *SLC30A8* | coding-missense | 0,969 | 0,798 | 1,177 | 0,751 | 0,972 | 0,872 | 1,084 | 0,614 | 3898 |
| rs10010131_G | G | 4 | *WFS1* | Intron | 1,138 | 0,950 | 1,362 | 0,160 | 0,999 | 0,902 | 1,108 | 0,992 | 3843 |
| rs5219_T | T | 11 | *KCNJ11* | coding-missense | 1,211 | 1,032 | 1,422 | **0,019** | 1,000 | 0,907 | 1,102 | 0,999 | 3595 |

**Table 7:**
Association of previously reported T2D loci with risk of GDM according to both criteria

| | | | | | WHO 1999 | | | | WHO 2013 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SNP** | **EA** | **Chr** | **Gene/nearest gene** | **Location** | **OR** | **CI(lower)** | **CI(upper)** | **p-value** | **OR** | **CI(lower)** | **CI(upper)** | **p-value** | **N** |
| rs2296172_G | G | 1 | *MACF1* | coding-missense | 0,925 | 0,711 | 1,204 | 0,562 | 1,043 | 0,896 | 1,213 | 0,588 | 3847 |
| rs340874_C | C | 1 | *PROX1* | Intergenic | 0,948 | 0,804 | 1,117 | 0,521 | 0,966 | 0,878 | 1,062 | 0,476 | 3709 |
| rs7578597_T | T | 2 | *THADA* | coding-missense | 0,906 | 0,729 | 1,127 | 0,377 | 0,927 | 0,808 | 1,063 | 0,277 | 3710 |
| rs243088_T | T | 2 | *BCL 11A* | Intergenic | 1,105 | 0,941 | 1,299 | 0,224 | 1,072 | 0,974 | 1,181 | 0,156 | 3717 |
| rs7593730_T | T | 2 | *RBMS1/ITGB6* | Intronic | 1,019 | 0,849 | 1,224 | 0,836 | 0,996 | 0,889 | 1,115 | 0,939 | 3906 |
| rs7607980_C | C | 2 | *COBL1* | coding-missense | 0,958 | 0,736 | 1,247 | 0,751 | 0,951 | 0,815 | 1,110 | 0,523 | 3885 |
| rs13389219_C | C | 2 | *GRB14* | Intergenic | 1,256 | 1,033 | 1,528 | **0,022** | 1,110 | 0,996 | 1,236 | **0,058** | 3829 |
| rs7578326_A | A | 2 | *KIAA1486/IRS1* | intron of uncharacterized LOC646736 | 0,974 | 0,800 | 1,184 | 0,789 | 0,985 | 0,878 | 1,105 | 0,795 | 3600 |
| rs2943641_C | C | 2 | *IRS1* | Intergenic | 0,927 | 0,767 | 1,120 | 0,432 | 0,977 | 0,874 | 1,092 | 0,679 | 3643 |
| rs4675095_A | A | 2 | *IRS1* | Intron | 1,113 | 0,871 | 1,422 | 0,391 | 1,040 | 0,905 | 1,196 | 0,580 | 3817 |
| rs831571_C | C | 3 | *PSMD6* | Intergenic | 1,029 | 0,845 | 1,252 | 0,777 | 0,935 | 0,833 | 1,051 | 0,261 | 3726 |
| rs4607103_C | C | 3 | *ADAMTS9-AS2* | Intron | 1,146 | 0,982 | 1,337 | **0,083** | 1,002 | 0,913 | 1,099 | 0,971 | 3884 |
| rs11920090_T | T | 3 | *SLC2A2* | Intron | 1,190 | 0,933 | 1,517 | 0,161 | 1,164 | 1,015 | 1,335 | **0,030** | 3606 |
| rs6815464_C | C | 4 | *MAEA* | Intron | 1,042 | 0,833 | 1,305 | 0,716 | 1,032 | 0,903 | 1,180 | 0,640 | 3722 |
| rs459193_G | G | 5 | *ANKRD55* | Intergenic | 0,990 | 0,841 | 1,167 | 0,908 | 1,072 | 0,972 | 1,181 | 0,163 | 3884 |
| rs4457053_G | G | 5 | *ZBED3* | intron of ZBED3-AS1 | 1,059 | 0,869 | 1,290 | 0,572 | 0,955 | 0,848 | 1,076 | 0,454 | 3579 |
| rs9470794_C | C | 6 | *ZFAND3* | Intron | 1,079 | 0,857 | 1,359 | 0,519 | 1,054 | 0,911 | 1,218 | 0,481 | 3608 |
| rs17168486_T | T | 7 | *DGKB* | Intergenic | 0,991 | 0,835 | 1,178 | 0,921 | 0,975 | 0,881 | 1,078 | 0,622 | 3855 |
| rs2191349_T | T | 7 | *DGKB/TMEM195* | Intergenic | 1,042 | 0,885 | 1,229 | 0,620 | 1,003 | 0,911 | 1,103 | 0,956 | 3903 |
| rs864745_T | T | 7 | *JAZF1* | Intron | 0,986 | 0,835 | 1,165 | 0,870 | 1,022 | 0,922 | 1,132 | 0,681 | 3876 |
| rs4607517_A | A | 7 | *GCK* | Intergenic | 1,046 | 0,826 | 1,324 | 0,708 | 1,013 | 0,881 | 1,164 | 0,861 | 3903 |
| rs17133918_T | C | 7 | *GRB10* | Intron | 1,038 | 0,871 | 1,238 | 0,675 | 0,976 | 0,880 | 1,083 | 0,651 | 3907 |
| rs933360_A | A | 7 | *GRB10* | Intron | 1,033 | 0,873 | 1,224 | 0,703 | 1,032 | 0,934 | 1,140 | 0,541 | 3905 |
| rs6943153_T | C | 7 | *GRB10* | Intron | 0,869 | 0,732 | 1,032 | 0,110 | 0,954 | 0,862 | 1,057 | 0,369 | 3602 |
| rs6467136_G | G | 7 | *GCC1-PAX4* | Intergenic | 1,119 | 0,955 | 1,311 | 0,166 | 0,977 | 0,890 | 1,073 | 0,625 | 3593 |
| rs516946_C | C | 8 | *ANK1* | Intron | 1,011 | 0,828 | 1,235 | 0,916 | 1,095 | 0,973 | 1,232 | 0,131 | 3922 |
| rs896854_T | T | 8 | *TP53INP1* | Intron | 0,976 | 0,833 | 1,143 | 0,759 | 0,973 | 0,885 | 1,069 | 0,570 | 3903 |
| rs7034200_A | A | 9 | *GLIS3* | Intron | 0,985 | 0,839 | 1,155 | 0,849 | 1,031 | 0,939 | 1,132 | 0,525 | 3868 |
| rs13292136_C | C | 9 | *TLE4 (CHCHD9)* | Intergenic | 0,946 | 0,757 | 1,183 | 0,628 | 0,982 | 0,861 | 1,121 | 0,793 | 3706 |
| rs12571751_A | A | 10 | *ZMIZ1* | Intron | 0,865 | 0,737 | 1,016 | **0,077** | 0,966 | 0,875 | 1,066 | 0,490 | 3601 |
| rs553668_A | A | 10 | *ADRA2A* | UTR-3 | 1,177 | 0,993 | 1,396 | **0,060** | 1,078 | 0,972 | 1,196 | 0,155 | 3666 |
| rs10885122_G | G | 10 | *ADRA2A* | Intergenic | 1,034 | 0,841 | 1,271 | 0,754 | 1,050 | 0,932 | 1,182 | 0,426 | 3683 |
| rs163184_G | G | 11 | *KCNQ1* | Intron | 0,903 | 0,762 | 1,070 | 0,237 | 1,001 | 0,908 | 1,104 | 0,980 | 3713 |
| rs2237895_C | C | 11 | *KCNQ1* | Intron | 0,964 | 0,817 | 1,137 | 0,664 | 1,013 | 0,920 | 1,116 | 0,790 | 3682 |
| rs11605924_A | A | 11 | *CRY2* | Intron | 0,840 | 0,721 | 0,979 | **0,025** | 1,009 | 0,920 | 1,106 | 0,854 | 3909 |
| rs7944584_A | A | 11 | *MADD* | Intron | 0,917 | 0,744 | 1,131 | 0,417 | 1,094 | 0,967 | 1,237 | 0,155 | 3553 |
| rs174550_T | T | 11 | *FADS1* | Intron | 0,947 | 0,763 | 1,175 | 0,621 | 0,964 | 0,851 | 1,092 | 0,568 | 3908 |
| rs1552224_A | A | 11 | *CENTD2* | Intergenic | 0,924 | 0,752 | 1,136 | 0,453 | 0,818 | 0,723 | 0,924 | **0,001** | 3911 |
| rs11063069_G | G | 12 | *CCND2* | Intergenic | 0,998 | 0,804 | 1,239 | 0,987 | 1,043 | 0,915 | 1,190 | 0,526 | 3671 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs10842994_C | C | 12 | *KLHDC5* | Intergenic | 1,138 | 0,896 | 1,445 | 0,289 | 0,971 | 0,846 | 1,114 | 0,671 | 3906 |
| rs1153188_A | A | 12 | *DCD* | Intergenic | 1,153 | 0,930 | 1,429 | 0,193 | 1,014 | 0,898 | 1,144 | 0,824 | 3912 |
| rs1531343_C | C | 12 | *HMGA2* | intron of pseudogene | 0,836 | 0,678 | 1,031 | **0,094** | 0,905 | 0,801 | 1,021 | 0,105 | 3915 |
| rs7961581_C | C | 12 | *TSPAN8,LGR5* | Intergenic | 0,917 | 0,775 | 1,085 | 0,314 | 1,026 | 0,928 | 1,136 | 0,614 | 3703 |
| rs7957197_T | T | 12 | *OASL/TCF1/HNF1A* | intron of QASL | 0,878 | 0,657 | 1,173 | 0,379 | 1,004 | 0,831 | 1,212 | 0,968 | 3924 |
| rs17271305_G | G | 15 | *VPS13C* | Intron | 1,020 | 0,860 | 1,209 | 0,819 | 0,928 | 0,837 | 1,029 | 0,158 | 3825 |
| rs11071657_A | A | 15 | *FAM148B* | Intergenic | 1,030 | 0,870 | 1,220 | 0,728 | 0,926 | 0,837 | 1,024 | 0,136 | 3897 |
| rs7177055_A | A | 15 | *HMG20A* | Intergenic | 1,001 | 0,851 | 1,177 | 0,994 | 0,985 | 0,896 | 1,081 | 0,745 | 3907 |
| rs11634397_G | G | 15 | *ZFAND6* | Intergenic | 0,894 | 0,761 | 1,049 | 0,169 | 0,966 | 0,878 | 1,063 | 0,478 | 3910 |
| rs8042680_A | A | 15 | *PRC1* | Intron | 0,894 | 0,764 | 1,047 | 0,164 | 0,997 | 0,904 | 1,100 | 0,958 | 3887 |
| rs7202877_T | T | 16 | *BCAR1* | Intergenic | 1,214 | 0,895 | 1,646 | 0,213 | 1,047 | 0,877 | 1,250 | 0,613 | 3915 |
| rs8090011_G | G | 18 | *LAMA1* | Intron | 0,955 | 0,815 | 1,119 | 0,571 | 0,931 | 0,847 | 1,022 | 0,134 | 3911 |
| rs10401969_C | C | 19 | *SUGP1* | Intron | 0,963 | 0,728 | 1,274 | 0,791 | 0,860 | 0,729 | 1,015 | **0,074** | 3605 |
| rs8108269_G | G | 19 | *GIPR* | Intergenic | 1,027 | 0,858 | 1,230 | 0,770 | 1,078 | 0,969 | 1,198 | 0,167 | 3508 |
| rs10423928_A | A | 19 | *GIPR* | Intron | 0,858 | 0,679 | 1,085 | 0,201 | 1,060 | 0,932 | 1,207 | 0,374 | 3911 |
| rs6017317_G | G | 20 | *FITM2-R3HDML-HNF4A* | Intergenic | 0,961 | 0,815 | 1,134 | 0,641 | 0,983 | 0,890 | 1,085 | 0,728 | 3758 |
| rs5945326_A | A | X | *DUSP9* | Intergenic | 0,957 | 0,816 | 1,121 | 0,583 | 1,016 | 0,921 | 1,122 | 0,745 | 3589 |

**Table 8**
Association of selected loci with insulin secretion (HOMA2-B)

| SNP | EA | Chr | Gene/nearest gene | Location | Beta | SE | p-value | N |
|---|---|---|---|---|---|---|---|---|
| rs340874_C | C | 1 | *PROX1* | Intergenic | 0,009 | 0,011 | 0,388 | 3395 |
| rs560887_C | C | 2 | *G6PC2/ABCB11* | Intron | -0,004 | 0,016 | 0,818 | 3578 |
| rs11708067_A | A | 3 | *ADCY5* | Intron | 0,024 | 0,012 | 0,053 | 3556 |
| rs11920090_T | T | 3 | *SLC2A2* | Intron | -0,014 | 0,015 | 0,361 | 3301 |
| rs4607517_A | A | 7 | *GCK* | Intergenic | 0,007 | 0,012 | 0,571 | 3372 |
| rs2191349_T | T | 7 | *DGKB/TMEM195* | Intergenic | -0,008 | 0,011 | 0,480 | 3575 |
| rs7034200_A | A | 9 | *GLIS3* | Intron | 0,002 | 0,016 | 0,922 | 3576 |
| rs10885122_G | G | 10 | *ADRA2A* | Intergenic | -0,006 | 0,010 | 0,546 | 3545 |
| rs7944584_A | A | 11 | *MADD* | Intron | -0,021 | 0,013 | 0,116 | 3372 |
| rs174550_T | T | 11 | *FADS1* | Intron | 0,011 | 0,014 | 0,435 | 3248 |
| rs7756992_G | G | 6 | *CDKAL1* | Intron | 0,011 | 0,014 | 0,446 | 3576 |
| rs11071657_A | A | 15 | *FAM148B* | Intergenic | 0,023 | 0,011 | 0,044 | 3568 |

**Table 9:**
Association with HOMA-IR selected loci: insulin resistance SNPs

| SNP | EA | Chr | Gene/nearest gene | Location | Beta | SE | p-value | N |
|---|---|---|---|---|---|---|---|---|
| rs2943641_C | C | 2 | *IRS1* | intergenic | -0,001 | 0,014 | 0,923 | 3337 |
| rs4675095_A | A | 2 | *IRS1* | intron | -0,028 | 0,017 | 0,102 | 3500 |
| rs4607517_A | A | 7 | *GCK* | intergenic | 0,018 | 0,018 | 0,299 | 3576 |
| rs7607980_C | C | 2 | *COBLL1* | coding-missense | -0,070 | 0,019 | 0,0001 | 3557 |
| rs13389219_C | C | 2 | *GRB14* | intergenic | 0,029 | 0,013 | 0,026 | 3518 |
| rs10423928_A | A | 19 | *GIPR* | intron | 0,041 | 0,016 | 0,012 | 3585 |

To assess whether changing the "cut-off"' value of glucose threshold applied for diagnosis of GDM changes the association of SNPs, different cut off values of glucose taken as different interpretations of WHO1999 and WHO2103 criteria used for defining GDM and their association with selected SNPs in this North Indian pregnant group was determined. GDM in subjects was defined by (i) FBS ≥ 5.1, (ii) FBS ≥7.0, (iii) 2-hour glucose ≥7.8, (iv) 2-hour glucose ≥ 8.5, (v) FBS ≥5.1 and 2 hour glucose ≥8 and (vi) FBS ≥7.0 and 2-hour glucose ≥7.8. . GDM prevalence according to these criteria is shown in fig. 13.

Various associations were observed for different SNPs at different glucose diagnostic values including SNPs rs7903146 of *TCF7L2* (p=0.045), rs1799999 of *PPIR3A* (p=0.029), and rs11063069 of *CCND2* (p=0.046) with GDM defined using FBS ≥5.1 AND 2-hour glucose ≥8.5 (supplementary table 5). SNP rs6467136 of *GCCI-PAX4* associated with GDM women defined using (i) only FBS ≥7.0 (p=0.010), (ii) 2-hour glucose ≥8.5 (p=0.044), and (iii) FBS ≥7.0 and 2-hour glucose ≥ 7.8 (p=0.005) (supplementary table 5).

Similarly, SNPs rs10401969 of *SUGP1* (p=0.031) with FBS ≥5.1, SNP rs459193 of *ANKRD55* (p=0.045) with FBS ≥7.0, rs6943153 of *GRB10* (p=0.040) with 2-hour glucose ≥8.5 associated with GDM (supplementary table 5). Further, significant associations were seen between GDM and SNPs rs17168486 of *DGKB* (p=0.039), rs2191349 of *DGKB/TMEM195* (p=0.017), and rs689 of *INS, INS- IGF2* (p=0.038) using "cut off" threshold as FBS ≥7.0 AND glucose ≥7.8 (supplementary table 5).

# Paper IV

*Phenotypic and genotypic differences between Indian and Swedish women with gestational diabetes mellitus.*

The prevalence of GDM in North Indian women residing in the state of Punjab was 3.11% defined by GDM criteria cut off followed in Sweden. The women in Sweden were >10 years older ($p=1.21x10^{-40}$) and had higher BMI (28.09 ± 0.64 vs. 24.08 ± 0.42, $p=3.76\ x10^{-07}$) than the pregnant women in Punjab recruited in the study. Indian women had higher fasting and 2 hour glucose values, lower fasting insulin and lower insulin secretion depicted as HOMA2-B and low insulin resistance depicted as HOMA2-IR adjusted for BMI and age, in comparison with GDM women from Sweden (table 1).

**Table 10.**
Clinical characteristics of Indian and Swedish women with GDM (diagnosed based on 2 hour glucose cut-offs >=10mmol/l). Mean ± SEM are represented. P-values are calculated based on inverse normal transformed data.

| | Swedish | N (Swedish) | Indian | N (Indian) | P value |
|---|---|---|---|---|---|
| Age | 31.78 ± 0.36 | 149 | 20.97 ± 0.33 | 125 | $1.21x10^{-40}$ |
| BMI | 28.09 ± 0.64 | 56 | 24.08 ± 0.42 | 125 | $3.76 x10^{-07}$ |
| Fasting glucose[a] | 4.79 ± 0.10 | 49 | 5.72 ± 0.15 | 125 | $1.60 x10^{-05}$ |
| 2 hour glucose[a] | 10.99 ± 0.08 | 149 | 12.07 ± 0.20 | 125 | $3.13 x10^{-02}$ |
| Fasting insulin[a] | 78.17 ± 12.67 | 51 | 51.8 ± 5.35 | 125 | $3.74 x10^{-06}$ |
| HOMA2-B[a] | 123.99 ± 7.55 | 45 | 76.61 ± 3.83 | 109 | $3.00 x10^{-09}$ |
| HOMA2-IR[a] | 1.26 ± 0.10 | 45 | 1.04 ± 0.10 | 109 | $1.11 x10^{-03}$ |

[a] adjusted for age and BMI

Six SNPs previously associated with GDM/T2D in Indian population based studies were assessed for association with GDM in Indian and Swedish women defined by Swedish GDM criteria. Risk allele C of rs7178572 SNP near *HMG20A* nominally associated with GDM in Indian but not in Swedish women (table 11). Another T2D risk genetic loci associated specific for Punjabi community known as Jat Sikhs, the Asp/Tyr missense variant of SNP rs1799999 in the *PP1RR3A* gene, revealed a trend towards significance in Indian subjects but not in Swedish women (table 11). The variant was also nominally associated with decreased 2-hour insulin in Swedish women (-β =-0.57 ± 0.22, p=0.02).

When assessed for SNPs previously associated with GDM/T2D in Europeans, the rs1111875 SNP near the *HHEX*/*IDE* genes nominally associated with GDM in Swedish women (p=0.031, table 11). The same SNP differed in frequency between Indian and Swedish women (p<0.0001, table 12). The risk allele of rs11708067 in *ADCY5* was also associated with increased 2-hour glucose (p= 0.037), decreased HOMA2-B (p=0.010) in Swedish GDM women (supplementary table 1). The same SNP was associated with 2 hour glucose in all Swedish women (GDM + non-GDM) (β = 0.12 ± 0.04, p=0.004).The T2D risk allele A of rs11605924 SNP in the intron of the *CRY2* gene was protective in the Indian population (OR = 0.67, p=0.0026) and was a risk variant in the Swedish women (OR=1.44, p=0.012).

Both the before mentioned SNPs showed significant differences in the major and minor allele frequencies between both populations (*ADCY5* SNP p<0.0001 and *CRY2* SNP p=0.0004) (table 12).

The rs8090011 SNP in intron of the *LAMA1* gene nominally associated with GDM risk (OR =1.49 (CI 1.11-2.01), p = 0.009) and lower 2 hour insulin levels in Swedish women (β -0.28 ± 0.13, p = 0.044). T2D/GDM risk SNPs rs12571751 in the intron of *ZMIZ1* (p=0,02), rs5945326 near *DUSP9*(p = 0.039), and rs2237895 in the intron of *KCNQ1* (p=0,02) nominally associated with GDM risk in Swedish women (table

11). The rs7593730 SNP near *RBMS1* was found to be associated with GDM risk in North Indian Punjabi women. Further, GDM risk alleles in rs560887 in *G6PC2* (p=0.0008), rs11708067 in *ADCY5* (p=0.005), rs10010131 in *WFS1* (p<0.0001) and rs10811661 (p=0.0073) in *CDKN2B* showed differences in frequencies when assessed for association with GDM in both Indian and Swedish women (table 12, fig. 15). Genetic risk scores (GRS) based on T2D/GDM loci predicted GDM risk in Indian (fig. 14a) but not Swedish women (fig. 14b). GRR for insulin resistance was 0.91±1.2, p=0.064 for Swedish, 0.04 (±1.2, p=0.25) for Indian women and for insulin secretion was -0.08 (±0.043, p=0.46) for Swedish and -0.008 (±0.037, p=0.83) for Indian women.

**Table 11.**
Association of previously reported GDM and T2D with risk of GDM in Indian and Swedish women. intervals.

| | | | | | | INDIA | | | SWEDEN | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **CHR** | **SNP** | **BP** | **Gene** | **Location** | **A1** | **N** | **OR (CI)** | **P** | **N** | **OR (CI)** | **P** |
| **15** | rs7178572 | 77454848 | *HMG20A/DUSP9* | intergenic | T | 3346 | 0.75 (0.57 - 0.98) | **0.03** | 476 | 0.8253 (0.59 - 1.15) | 0.25 |
| **10** | rs1111875 | 92703125 | *HHEX/IDE* | intergenic | G | 3675 | 1.02 (0.79 - 1.32) | 0.86 | 443 | 0.71 (0.52 - 0.97) | **0.031** |
| **3** | rs11708067 | 123346931 | *ADCY5* | intron | G | 3648 | 1.29 (0.97 - 1.71) | 0.084 | 466 | 0.69 (0.48 -1.00) | 0.054 |
| **11** | rs11605924 | 45851540 | *CRY2* | intron | A | 3679 | 0.67 (0.52 - 0.87) | **0.003** | 484 | 1.44 (1.08-1.91) | **0.013** |
| **10** | rs12571751 | 79182874 | *ZMIZ1* | intron | G | 3390 | 1.24 (0.95 - 1.61) | 0.11 | 492 | 1.39 (1.05-1.83) | **0.021** |
| **11** | rs2237895 | 2835964 | *KCNQ1* | intron | C | 3463 | 0.81 (0.62 - 1.06) | 0.13 | 410 | 1.43 (1.06-1.94) | **0.020** |
| **2** | rs243088 | 60341610 | *BCL11A* | intergenic | T | 3497 | 1.29 (0.99 - 1.68) | 0.06 | 425 | 1.13 (0.83-1.55) | 0.41 |
| **X** | rs5945326 | 153634467 | *DUSP9* | intergenic | G | 3377 | 1.15 (0.88 - 1.50) | 0.29 | 495 | 0.69 (0.49-0.98) | **0.035** |
| **15** | rs7177055 | 77540420 | *HMG20A* | intergenic | G | 3680 | 0.74 (0.57 - 0.96) | **0.024** | 457 | 0.91 (0.65-1.27) | 0.58 |
| **2** | rs7593730 | 160314943 | *RBMS1/ITGB6* | intronic | T | 3673 | 0.87 (0.63 - 1.21) | **0.40** | 457 | 0.97 (0.68-1.37) | 0.86 |
| **18** | rs8090011 | 7068463 | *LAMA1* | intron | G | 3683 | 1.02 (0.79 - 1.32) | 0.89 | 457 | 1.49 (1.11-2.01) | **0.009** |

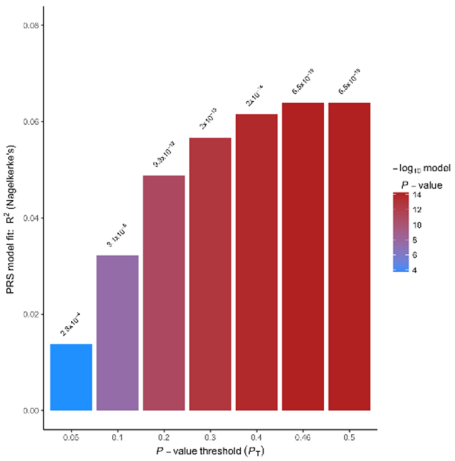
OR = odds ratio, CI = confidence

**Table 12.**
Allele frequency comparison of previously reported GDM loci in Indian and Swedish women with GDM (Swedish diagnosis criteria).

| | | INDIA | | | | | | SWEDEN | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CHR | **SNP** | **Minor/ Major** | **N** | **Minor N** | **MAF** | **Major N** | **MajAF** | **Minor/ Major** | **N** | **Minor N** | **MAF** | **Major N** | **MajAF** | **P** |
| **2** | rs560887 | A/G | 244 | 32 | 0.1311 | 212 | 0.8689 | A/G | 192 | 50 | 0.2604 | 142 | 0.7396 | **0.0008** |
| **3** | rs11708067 | G/A | 246 | 67 | 0.2724 | 179 | 0.7276 | G/A | 256 | 43 | 0.168 | 213 | 0.832 | **0.005** |
| **3** | rs4402960 | T/G | 242 | 93 | 0.3843 | 149 | 0.6157 | T/G | 176 | 56 | 0.3182 | 120 | 0.6818 | 0.1794 |
| **4** | rs10010131 | A/G | 242 | 62 | 0.2562 | 180 | 0.7438 | A/G | 224 | 100 | 0.4464 | 124 | 0.5536 | **<0.0001** |
| **6** | rs7754840 | C/G | 232 | 73 | 0.3147 | 159 | 0.6853 | C/G | 232 | 79 | 0.3405 | 153 | 0.6595 | 0.621 |
| **6** | rs7756992 | G/A | 230 | 70 | 0.3043 | 160 | 0.6957 | G/A | 234 | 70 | 0.2991 | 164 | 0.7009 | 0.9197 |
| **8** | rs13266634 | T/C | 244 | 56 | 0.2295 | 188 | 0.7705 | T/C | 260 | 69 | 0.2654 | 191 | 0.7346 | 0.3555 |
| **9** | rs10811661 | C/T | 244 | 32 | 0.1311 | 212 | 0.8689 | C/T | 224 | 26 | 0.1161 | 198 | 0.8839 | **0.0073** |
| **9** | rs2796441 | T/C | 244 | 106 | 0.4344 | 138 | 0.5656 | T/C | 252 | 106 | 0.4206 | 146 | 0.5794 | 0.7857 |
| **10** | rs1111875* | G/A | 240 | 107 | 0.4458 | 133 | 0.5542 | A/G | 242 | 85 | 0.3512 | 157 | 0.6488 | **<0.0001** |
| **11** | rs5219 | T/C | 234 | 92 | 0.3932 | 142 | 0.6068 | T/C | 126 | 58 | 0.4603 | 68 | 0.5397 | 0.2203 |
| **11** | rs11605924* | A/C | 240 | 94 | 0.3917 | 146 | 0.6083 | C/A | 270 | 121 | 0.4481 | 149 | 0.5519 | **0.0004** |

N =total number of alleles, minor_n = total number of minor alleles, MAF = minor allele frequency, MajAF = major allele frequency, p = p-value for the frequency differences between India and Sweden.
*Minor and major alleles are reversed

14(A)




14(B)

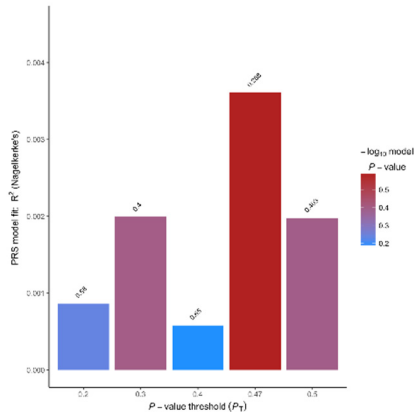



**Figure 14**
Bar plot from PRSice showing results at broad *P*-value thresholds for T2D polygenic risk scores predicting GDM in (A) Indian and (B) Swedish women. (A) is indicative of a role of common T2D genetic risk variants in GDM etiology in the Indian population.

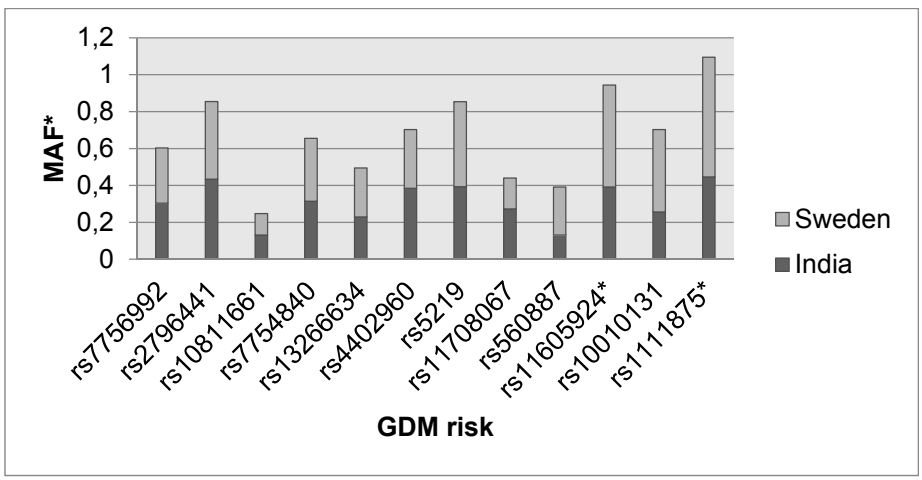



**Figure 15**
Frequencies of minor alleles (as defined in EUR population) of previously reported GDM loci in Indian and Swedish women with GDM. rs11605924 and rs 1111875 showed an interchange of major and minor alleles in Indian GDM women.

# Discussion

The overarching aim of the current thesis was to address key aspects of the epidemiology and pathophysiology including the role of genetic versus non-genetic factors on the risk of developing GDM in North India. The project kicked off as a World Diabetes Foundation (WDF) sponsored GDM awareness and educational program, but driven by scientific curiosity and a true pioneering spirit, the project soon developed into a state-of-the art epidemiological study of the prevalence and risk factors of GDM in North India using two different and somewhat controversial WHO1999 versus WHO2013 criteria. Due to limited financial resources and poorly established research infrastructure, the study set-up was simplistic and adapted to the experimental conditions to ensure feasibility as well as optimal quality of data for the chosen setting. The local implementation of the study was entirely driven by the author of this thesis relying on in depth knowledge about the local health care system, personal connections and a systematic training and supervision of the health care professionals that performed the physical examinations. The examinations of the pregnant women was kept a minimum of what is required to address the key questions of the project, including a standard questionnaire, a standard 75 gram oral glucose tolerance test as well as a fasting blood sample for measurements of serum insulin levels and extraction of DNA. Plasma and serum glucose and insulin levels were measured at local laboratories while DNA extraction and analyses was performed in Sweden after appropriate permissions. The systematic and persistent approach ensured the successful examination of around 5000 pregnant women from different rural and urban sites in Punjab, North India, which key results are discussed in the following.

As a first and foremost important finding, we showed that the prevalence of GDM increased from 9% to no less than 35% when using the most recent proposed WHO2013 criteria as compared with the previous WHO 1999 criteria (201). These figures were in the same magnitude as results from a Norwegian GDM screening study including non-Caucasian women of Asian origin (125). Indeed such alarming figures stigmatizing more than a third of all North Indian pregnant women with a diagnosis of GDM needs careful consideration with respect to whether the proposed WHO2013 GDM criteria should be generally adopted in a resource low Indian health care system. The rationale behind the WHO2013 GDM criteria with its lower fasting plasma glucose cut off levels was the finding from the HAPO study that no

lower cut off levels could be identified for the association between fasting plasma glucose on one side and prevalence of maternal pregnancy complications as well as children malformations on the other side (111). However, despite the knowledge from clinical trials that lowering plasma glucose in GDM women diagnosed by previous and less inclusive criteria is associated with improved pregnancy outcomes for both mother and child, this may not necessarily be the case for glucose lowering treatment in women diagnosed by the much more inclusive WHO2013 criteria. To this end, the finding of an association between fasting plasma glucose levels and pregnancy outcomes even in the lowest near normal range of the scale does not necessarily mean that mild elevations of plasma glucose levels are the direct cause of pregnancy complications. In particular, common risk factors of GDM including adiposity, age and social status are also recognized risk factors of pregnancy complications irrespective of plasma glucose levels. Therefore, residual confounding by unknown non-glucose pregnancy risk factors may account for the association between plasma glucose levels at the lowest level of the scale on one side, and pregnancy complications on the other side. There is a need for a state-of-the-art randomized intervention study of intensive versus less intensive glucose lowering treatment in GDM women diagnosed by the WHO2013 criteria before general implementation of the these criteria can be recommended.

A potential influence of unknown confounding factors operating primarily in the lowest range of the scale may also explain our finding that different risk factors including obesity, age, vegetarian diet, illiteracy and religion affected fasting versus 2 hours post oral glucose challenge plasma glucose levels in a differential manner (201). This as well as the differential influence of these risk factors on GDM defined by the WHO1999 versus the WHO2013 criteria was discussed in depth in our initial cohort publication (202). Interestingly, a strong family history of diabetes was reported in more than a third of all women in the study including both GDM as well as non-GDM women by both criteria (201). Accordingly, family history of diabetes was therefore to our surprise not identified as an independent risk factor for GDM using either WHO 1999 or WHO 2013 criteria among North Indian women. The explanation for this remains unknown but actually not inconsistent with our genetic findings as mentioned in Paper 3 and 4manuscripts and discussed below.

In the second publication of our North Indian GDM screening study we found evidence of impaired insulin secretion in GDM as classified by both the WHO1999 and WHO2013 criteria as compared with women classified as having a normal glucose tolerance by the respective criteria. These findings were in general cohesive with observations made by Nocter et al (225). Interestingly, women classified as having a normal glucose tolerance by the adapted WHO2013 criteria appeared metabolically healthier than normal glucose tolerant women by the WHO1999 criteria (table 1). The extent to which this influences the risk of short and long term

pregnancy complications in mother and offspring of pregnancies classified by the different criteria needs more extensive evidence based studies.

Another interesting finding was that the average fasting plasma glucose level among women with GDM by the WHO1999 criteria was slightly lower than in women diagnosed GDM with the adapted WHO2013 criteria. The explanation for this may as discussed previously be that women diagnosed GDM with the adapted WHO2013 criteria women qualified for their diagnosis due to elevated fasting plasma glucose levels (n=1779). In contrast, the majority of women with GDM by the WHO1999 criteria qualified for their diagnosis due to increased 2-hour post OGTT plasma glucose levels (n=458)(201). This difference may explain the lower insulin secretion in adapted GDM2013 compared with GDM1999 cases. Increased BMI and age were associated with increased insulin resistance and with a (possibly compensatory) increased insulin secretion until age 30 years hereafter insulin secretion declined (table 2).

Using regression analyses we furthermore documented that the same risk factors shown to influence GDM by the two criteria in a differential manner also influence the two major pathophysiological relevant defects in GDM, impaired insulin secretion and insulin resistance, in a differential manner (202).

As for the potential genetic contribution to the pathophysiology of GDM, we found that a family history of diabetes was exclusively associated with insulin resistance and not with impaired insulin secretion (225). Indeed, this finding is in line with previous studies of first degree relatives of patients with T2D (226). However, this finding is not in agreement with findings from genome-wide association studies of the majority of T2D susceptibility SNPs are associated with impaired insulin secretion rather than insulin resistance (227). This may be explained by the concept of heritability to be confounded by non-genetic shared risk factors of GDM in some families, which in the case of a weak (or even absent) true genetic component falsely appear as a genetic component.

Considering the common underlying genetic basis of GDM and T2D, in paper 3, we investigated the association of previously reported common (1) T2D (2) GDM and (3) T2D / GDM loci from Indian population based studies with GDM in the current study population. Very few studies have investigated the genetic architecture of T2D and GDM in the Indian population, and to our knowledge, no previous studies have investigated genetics of GDM in the North Indian population and in such a large scale in the world. (186,188,223,228).

Two SNPs in *HMG20A* and *HNF4A* previously associated with T2D risk in Asian Indian population and GDM risk in South Indian population (223) here did not associate with GDM in the Punjabi pregnant women regardless of diagnosis criteria. The North Indian pregnant women being studied here belongs to the "Ancestral

North Indians" (ANI) group and is genetically similar to Middle Eastern, Central Asian and European populations whereas the South Indian population belongs to "Ancestral South Indian" (ASI) group, which is distinct from the ANI and East Asian groups. It is possible that the differences in allele frequencies between North and South Indian groups be the reason why we didn't see the association (229). This was evident with different frequency rates of risk allele G in *HMG20A* SNP rs7178572 and A in *HNF4A* SNP rs4812829 (52.08% and 28.97% in North Indians and 46.1% and 35.15% in South Indians respectively).

Notably, there were no associations demonstrated in this group for T2D or GDM risk genetic variants selected from previously replicated study reports in European or Indian populations in either criterion. The association of T2D risk SNPs in *CDKAL1* and *MTNR1B* on GDM is based on the only GWAS study thus far and was conducted on the Korean population. At least 2 previous candidate gene studies, one based on the Danish and another on Norwegian women, have shown the association of some T2D risk loci with GDM risk (186,,228) Another replicated genetic risk variant for T2D and GDM association is *MTNR1B* which has shown significant association with GDM in the Norwegian population(228).The CDK5 regulatory subunit associated protein 1 like 1 coding gene *CDKAL1* is expressed in pancreas, skeletal muscle and brain and specifically inhibits activity of the serine / threonine protein kinase cyclin-dependent kinase 5 (CDK5). CDK5 activation leads to inhibition of insulin secretion, particularly in a high glucose environment (230) Inhibition of this activity could protect pancreatic beta cells from glucotoxicity (231). The T2D risk variant in the melatonin receptor 1B coding *MTNR1B* gene modulates insulin release and melatonin treatment inhibited insulin secretion, with risk allele carriers exhibiting higher glucose levels In this present work, we did not find any association of *MTNR1B* variants or any of the other GDM or T2D risk variants with risk of GDM this Punjabi pregnant women cohort. This could suggest other alternate mechanisms as potential cause of GDM in this specific North Indian pregnant Punjabi population group.

Paradoxically, theT2D genetic risk loci in *CRY2* (WHO1999), *CENTD2* (WHO2013), and *ADCY5* (WHO2013) were protective against GDM in Punjabi women. T2D risk variants in the *CRY2* (WHO1999), *CENTD2* (WHO2013) and the *ADCY5* (WHO2013) genes were here protective for GDM. *CRY2* codes for the cryptochrome protein is involved in the regulation of the circadian clock. Risk allele carriers of the rs11708067 SNP in *ADCY5* has been previously shown to reduce *ADCY5* expression in pancreatic beta cells. In addition, *ADCY5* played a key role in coupling glucose to insulin secretion in human islets (232). Here, we also found 3 insulin resistance loci (C allele in rs7607980 in the *COBLL1*, rs13389219 in *GRB14* and rs10423928 in *GIPR*) among 6 previous reported insulin resistance loci, demonstrated an association with HOMA2-IR in these women., The C allele in rs7607980 in the *COBLL1* gene previously associated with lower serum insulin and

insulin resistance in overweight and obese children (233).*COBLL1* codes for Cordon-Bleu WH2 Repeat Protein Like 1 protein. rs13389219 near the growth factor receptor bound protein 14 coding *GRB14* and rs10423928 in the gastric inhibitory polypeptide receptor coding *GIPR* also here associated with HOMA2-IR. To our knowledge, this is the first report of insulin resistance loci during pregnancy in the North Indian population. When more stringent interpretation of WHO1999 criteria ('AND' for both fasting and 2-hour glucose cut –off diagnostic values) is applied, one of the robust association of T2D genetic risk loci in *TCF7L2*, becomes significant for GDM in this North Indian cohort, which in turn suggested that GDM in North Indians align with impaired glucose tolerance in European population group. SNPs at *ANKRK55*, *GRB10* and 2 SNPs at the *DGKB* locus were also found to be associated with GDM as new genetic risk loci in this population group of pregnant Punjabi women. These findings may suggest that more stringent definition of current GDM diagnostic criteria are closer to T2D in a given population.

The 4$^{th}$ manuscript was a comparative study of GDM between Indian and Swedish populations. Here we standardized the diagnosis criteria for GDM in the Indian population to the Swedish cut-offs i.e., 2-hour glucose >=10mmol/l due to availability of data in the Swedish cohorts. Despite being on average 10 years younger, a higher prevalence of GDM was seen in the North Indian population compared to the previous reports on the Swedish women (3.11 and 2.6%respectively. (234). This is in alignment with results of previous studies that report higher the prevalence of T2D in a given population, higher the prevalence of GDM in the same group (235) India has also been reported to exhibit slightly higher prevalence of T2D in comparison with Sweden (8.8% vs. 6.8% (236,237). The Indian pregnant women in the current study were younger and had a lower average BMI than the Swedish GDM women. Despite this, however, they had higher fasting and 2-hour plasma glucose values, lower fasting insulin levels, lower insulin secretion as well as lower degree of insulin resistance. There is a significant association reported between BMI and insulin resistance (238) and therefore the differences depicted between Indian and Swedish women in insulin resistance could be attributed to BMI (Fig.1), wherein Swedish women had higher BMI and thus higher insulin resistance. It can be concluded that with low BMI and optimal insulin sensitivity, the defects in insulin secretion, supported by lower HOMA-B, was a dominant factor in Indian GDM women whereas insulin resistance was a more prevalent cause for GDM in Sweden.

To ascertain the genetic basis for these differences, we first assessed the association of 6 loci previously associated with T2D or GDM in India. The rs7178572 SNP near *HMG20A* associated with GDM in Indian while applying higher glucose threshold cut-off defined by WHO 1999 criteria, however this association was not seen in Swedish women. This SNP was previously associated with T2D in European populations. While earlier studies showed a weak association of rs7178572 with

*PSTPIP1* expression in lymphoblastoid cell lines, we here showed that rs7178572 significantly influences the expression of both *PSTPIP1* and *HMG20A*, thereby indicating that both could be causal. Proline-Serine-Threonine Phosphatase Interacting Protein 1 coding *PSTPIP1* gene is a tyrosine phosphatase that inhibits T-cell activation upon T-cell receptor (TCR) and CD28 engagement, irrespective of CD2 co-stimulatory effect (239). The high mobility group protein coding HMG20A showed higher expression in islets compared to muscle and adipose tissue and a transient increase in expression levels were observed upon glucose stimulation. HMG20A was downregulated in T2D and T1D islets, and knockdown decreased expression of *NEUROD*, *INS* and *GK* with an accompanying impairment in GSIS (240). Therefore, this could be a more plausible candidate gene in GDM etiology.

The previously reported GDM and T2D locus rs1111875 near HHEX/IDE was here associated with GDM risk in Swedish women whereas it revealed no association with GDM in the Indian population. The T2D risk SNP rs11605924 in *CRY2* had opposite effect in both groups. Thus, it was a protective against GDM in North Indian but in contrast conferred increased risk of GDM in the Swedish women. *CRY2* encodes the circadian rhythm gene cryptochrome 2, and is a target for the *CLOCK-BMAL1*, which are core components of the endogeneous clock. The *CRY2* variant associated with fasting plasma glucose levels and reduced liver fat content in human liver in a previous study (233), and the CRY2 mRNA expression associated with hepatic triglyceride content indicating that *CRY2* could represent a modulator in liver metabolism which promotes triglyceride storage and reduced glucose production (241). Interestingly, the protective effect of the T2D risk allele in the Indian population is suggestive of a different mechanism of GDM causation.

We could not find any overlaps between the GDM risk loci between Indian and Swedish populations. This could be indicative of differences in disease mechanisms, or alternately, due to limitations in study statistical power. The differences in frequencies were seen in 6 out of 12 GDM risk alleles, where 2 of them had reversal of major and minor alleles. One of the studies conducted previously determined 12 T2D risk alleles in 5 or more population groups that shared a stable pattern of decreasing frequencies from Africa through Europe to East Asia those were statistically significant. This declining effect seen in frequencies caused differentiation of T2D genetic risk showing higher in the Africans and lower in Asians, which was significant. The environment's unstable energy intake and its appropriate usage, and promotion of energy storage were thought to be causal mechanisms for these differences in different populations (242). Future studies and evidence will be needed to dissect such mechanisms, and *CRY2* could be considered as potential candidate gene as an example for the same.

# Summary and general conclusion

*Paper I*

The prevalence of GDM was 35% using WHO 2013 criteria vs. 9% using WHO 1999 criteria. Environmental risk factors urban habitat, illiteracy, non-vegetarianism, increased BMI, Hindu religion and low adult height were all independent risk factors of GDM using the 1999 criteria, whereas only urban habitat, low adult height and increased age were independent risk factors of GDM using the 2013 criteria. If WHO 2013 criteria is implemented in North India for the diagnosis of GDM, there would be more than one third of women (four-fold increase in prevalence) suffering for the same and this might have strong social consequences and stigmata for a young woman in Indian system. More evidence based studies are needed to identify screening risk factors, genetic determinants and short and long term clinical outcomes of treatment against GDM using WHO2013 criteria in Indian population.

*Paper II*

In this North Indian pregnant Punjabi women, GDM defined by both GDM1999 and adapted GDM2013 criteria are associated with impaired insulin secretion, but when categorized by the adapted GDM2013 criteria alone, association is by insulin resistance. Further evidence based data studying the interaction between genetic and environmental risk factors predisposing to GDM in this group of North Indian women compared with women of other ethnic origin is needed to understand underlying metabolic and genetic pathways, their implications and associations of glycaemia with GDM defined using WHO2013 and WHO1999 criteria.

*Paper III*

Some common genetic basis for T2D and GDM was observed and few novel associations were demonstrated in this population group whereas most common genetic loci for GDM discovered through studies based on European population seemed to not associate with GDM in North India. Furthermore, the surprising protective effect of some T2D risk loci is indicative of different mechanisms underlying GDM etiology in North India. Also, association depicted (e.g. *TCF7L2 )* when more stringent criteria threshold was used , suggest that more stringent

definition of current GDM diagnostic criteria are closer to T2D in a given population.

*Paper IV*

The exploration of phenotypic and genetic differences between pregnant women with GDM from India and Sweden showed Indian women had higher prevalence of GDM (compared to previous report), lower insulin secretion and better insulin sensitivity than Swedish women. The India specific rs7178572 SNP in the *HMG20A* gene nominally associated with GDM in Indian cohort as well but not in Swedish women. Genetic and non-genetic factors influencing glucose intolerance during pregnancy may depend upon ethnicity and given population group.

It is of paramount importance to explore the causes of and epidemiology of gestational diabetes and type 2 diabetes mellitus in different ethnic populations, especially in developing nations like India, where women are more susceptible and at increased risk of these diseases. Genetics factors may interact with environmental factors to manifest GDM or T2D in a given ethnic group. It is clear that the underlying mechanisms of GDM could vary between populations and therefore caution should be employed while applying standard criteria based on European populations to Indian women.

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*'Five-Golden ‘’ inspirational quotes:*

The best way to find yourself is to lose yourself in the service of others.

Strength does not come from physical capacity it comes from an indomitable will.

Glory lies in the attempt to reach one's goal and not in reaching it.

A man is but the product of his thoughts. What he thinks he becomes.

Be the change you want to see in the world.

Mahatma Gandhi

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***'Karmanye vaadhika raste, Maa faleshu kadachana Maa karafalaheturbhu, Matresagotsva Karmani' (****"No matter what conditions you encounter in life, your right is only to the works and not to the fruits thereof. You should not be impelled to act for selfish reasons, nor should you be attached to inaction.")*

***-- message from Bhagawad Gita ( Holy Book Mythological teachings, 700 words Hindu scripture in Sanskrit)***

# Popular Science Summary

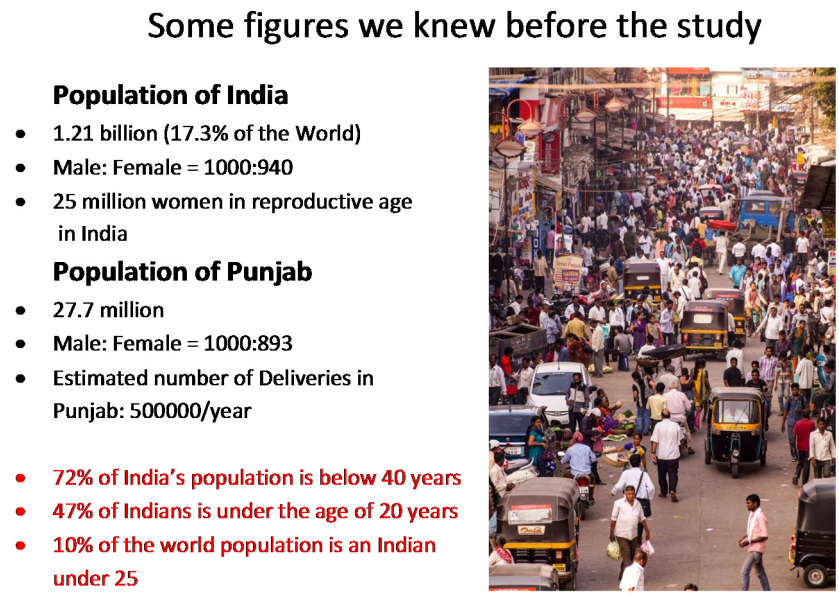


**Figure 16.**
Collected data from Government office during the study.

Diabetes is a colossal worldwide health problem. The latest estimate by World Health Organization (WHO) is that at there are 415 million adults between the age of 20-79 years with diabetes globally and by 2040, the prevalence of diabetes may rise to 642 million worldwide. Developing countries like India will bear the brunt of Diabetic Epidemic in the 21$^{st}$ century with almost 80% of all new cases of diabetes expected to appear by 2025. The picture of Diabetes in India is considerably different from that seen in the developed countries or west, for which most information is available. The aim eyes upon "identifying, aiding, assisting & treating" with latest knowledge & to formulate strategies at prevention levels. What concern us more is to prevent this epidemic at primary prevention level. As rightly commented "No single period in human development provides a greater potential (than pregnancy) for long range 'pay off" via a relatively short range period of enlightened metabolic manipulation.

Women in India with glucose intolerance during pregnancy are the most ideal group for understanding and prevention of rising numbers of diabetes. All forecasts indicate that Asia will see an explosive increase in diabetes and Gestational Diabetes (GDM).As an introduction to entity called GDM, clinical studies in diabetes & pregnancy during the past few decades have brought about the new concept of recognition of abnormal glucose metabolism occurring first time during pregnancy, which may be responsible for increased fetal losses. Furthermore, the diagnosis of this transient abnormal glucose tolerance customarily called gestational diabetes allows for identification of a group of patients who are at risk for developing established diabetes at a later stage of life. The abnormal tolerance is mainly due to altered carbohydrate metabolism during pregnancy because of placenta serving as an added endocrine organ responsible for insulin removal by secreting enzyme insulinase & also by production of certain insulin like hormones like human placental lactogen, oestrogen & progesterone, which blunts action of insulin. Thus, GDM is a over-expression of normal physiological action of pregnancy and unhealthy state with high blood glucose. Unfortunately, our knowledge of the blood glucose values that distinguishes the unhealthy GDM condition from normal pregnancy is limited and based on arbitrary thresholds associated with increased health risks in mother and child. The prevalence of GDM in a population corresponds to prevalence of T2D in the same group. Gestational Diabetes mellitus and its diagnostic criteria has been the subject of considerable controversy. The criteria for the diagnosis of GDM that were previously applied were not designed to identify pregnant women who are at increased risk for adverse prenatal outcomes but rather women who are at high risk for the development of diabetes after pregnancy. The prevalence of GDM differs in different population groups depending upon the diagnostic criteria used to define them. Demographic risk factors, genes and ethnic differences p lay a major part in development of T2D and GDM. Ethnically, Indian women have a high prevalence of diabetes and the relative risk of developing GDM in South Indian women is 11.3 times compared to white women. All forecasts indicate that Asia will see an explosive increase in diabetes and GDM. This dissertation addresses the problem of GDM in Asia and is based on epidemiological screening of 5,000 pregnant women in Punjab, northern India. For diagnosis of GDM, both WHO 1999 and newly endorsed and adapted WHO 2013 (with different 'cut-off glucose threshold' value for diagnosis) definitions were used. Different women defined GDM with different criteria.

WHO 2013 criteria increase the incidence of GDM from 95 (WHO 1999) to 35% of all pregnant women. Insulin deficiency plays a greater role than insulin resistance in GDM pathophysiology. Apart from insulin hormone, the influence of environmental risk factors like age, body mass index -BMI (height and weight), family history of T2D, diet (vegetarian and non-vegetarian), area of residence (town and village), religion (Hindu and Sikh) and education (literate or illiterate) , and

various genetic risk factors ( previously reported as genetic risk variants for T2D and GDM ) had crucial role in the risk of development of GDM.

In our genetic analysis, 79 genetic variables (commonly studied as risk factors), 12 of them in India showed clear differences in genetic and non-genetic causes of GDM between Indian women and women from Sweden. Very few genetic risk variables associated with risk of GDM in this North Indian women group. Interestingly, these women showed unique genetic architecture as compared with rest of the data available for different population groups from across the world. In one commonly known genetic variant for increased GDM risk in other population and more specifically for Swedish women, it was found that the same genetic variant instead protected these North Indian women being studied for GDM risk. The association of genes with GDM in Indians was different from rest of the populations studied so far in various countries.

In summary, the results underline the need to dissect further larger prospective surveys of women with GDM and their children in different ethnic groups to understand the complex relationship between risk factors and health risks in different parts of the world. We also need to better understand the connection between diagnostic criteria (displaying different cut off glucose threshold values) and health risks and develop better means to prevent GDM and its consequences for mother and child for future and coming generation.

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**Supplementary table 1.**
T2D associated SNPs selected from previously published GWAS studies upto 2012 and GDM associated loci (*) from previous candidate and GWAS studies.

| SNPs | GENE / nearest Gene | location | Chr | Locus | RA | OA | RAF | Trait | References |
|---|---|---|---|---|---|---|---|---|---|
| rs10923931 | *NOTCH2* | intron | 1 | 1p12 | T | G | 0.10 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs2296172 | *MACF1* | coding - missense | 1 | 1p34.3 | G | A | | T2D | A. Albrechtsen et al, Diabetologia, 2013 |
| rs340874 | *PROX1* | intergenic | 1 | 1q41 | C | T | 0.45 | Fasting glucose / insulin secretion / T2D | Dupuis et al Nat Genet 2010 |
| rs243021 | *BCL11A* | intergenic | 2 | 2p16.1 | A | G | 0.46 | T2D | Voight et al DIAGRAM 2010 |
| rs243088* | *BCL11A* | intergenic | 2 | 2p16.1 | T | A | 0.45 | T2D / GDM | Morris, naturegenetics 2012 |
| rs7578597 | *THADA* | coding - missense | 2 | 2p21 | T | C | 0.90 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs3923113 | *GRB14* | intergenic | 2 | 2q24.3 | A | C | 0.64 (0.74) | T2D | Kooner natgen 2012; Morris natgen, 2012 |
| rs13389219 | *GRB14* | intergenic | 2 | 2q24.3 | C | T | 0.60 | T2D | Morris, naturegenetics 2012 |
| rs7607980 | *COBL1* | coding - missense | 2 | 2q24.3 | C | T | | T2D | A. Albrechtsen et al, Diabetologia, 2013 |
| rs560887 | *G6PC2/ABCB11* | intron | 2 | 2q31.1 | C | T | 0.67 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs7578326 | *KIAA1486/IRS1* | intron of uncharacterized LOC646736 | 2 | 2q36.3 | A | G | 0.64 | T2D | Voight et al DIAGRAM2 2010 |
| rs2943641 | *IRS1* | intergenic | 2 | 2q36.3 | C | T | 0.63 | Fasting insulin /T2D / insulin sensitivity | Rung et al. Nat Genet 2010 |
| rs4675095 | *IRS1* | intron | 2 | 2q36.3 | A | T | 0.94 | fasting glucose/ insulin sensitivity | Dupuis et al Nat Genet 2010 |
| rs7593730* | *RBMS1/ITGB6* | intronic | 2 | 9q24.2 | T | C | 0.23 | T2D / GDM | Qi et al. Hum Molec Gen. 2010 |
| rs4607103 | *ADAMTS9-AS2* | intron | 3 | 3p14.1 | C | T | 0.76 | T2D / GDM | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs831571 | *PSMD6* | intergenic | 3 | 3p14.1 | C | T | 1 (0.688) | Asian T2D | Cho natgen 2012 |
| rs1801282 | *PPARG* | coding - missense | 3 | 3p25.2 | C | G | 0.86 | T2D / Insulin sensitivity | DGI, MIT and LU, Science 2007 |
| rs11708067* | *ADCY5* | intron | 3 | 3q21.1 | A | G | 0.77 | T2D / 2hr glucose / Fasting Glucose / HOMA B / GDM | Saxena et al. Nat Genet 2010 |
| rs11920090 | *SLC2A2* | intron | 3 | 3q26.2 | T | A | 0.86 | Fasting glucose / HOMA B | Dupuis et al Nat Genet 2010 |
| rs4402960 | *IGF2BP2* | intron | 3 | 3q27.2 | T | G | 0.29 | T2D | DGI, MIT and LU, Science 2007 |

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|---|---|---|---|---|---|---|---|---|---|
| rs10010131 | *WFS1* | intron | 4 | 4p16.1 | G | A | 0.60 | T2D | Sandhu et al nature genetics 2007, Lyssenko et al, NEJM 2008 |
| rs6815464 | *MAEA* | intron | 4 | 4p16.3 | C | G | 0.522 - 0.64 | Asian T2D | Cho natgen 2012 |
| rs459193 | *ANKRD55* | intergenic | 5 | 5q11.2 | G | A | 0.70 | T2D | Morris, naturegenetics 2012 |
| rs4457053 | *ZBED3* | intron of ZBED3-AS1 | 5 | 5q13.3 | G | A | 0.26 | T2D | Voight et al DIAGRAM2 2010 |
| rs9470794 | *ZFAND3* | intron | 6 | 6p21.2 | C | T | 0.50 (0.20) | Asian T2D | Cho natgen 2012 |
| rs7754840 | *CDKAL1* | intron | 6 | 6p22.3 | C | G | 0.30 | T2D | Steinthorsdottir, Nat Gen 2007, DGI, MIT and LU, Science 2007 |
| rs7756992 | *CDKAL1* | intron | 6 | 6p22.3 | G | A | 0.25 | T2D | Steinthorsdottir, Nat Gen 2007 |
| rs4607517 | *GCK* | intergenic | 7 | 7p13 | A | G | 0.20 | Fasting glucose/T2D / insulin sensitivity / HOMA B | Dupuis et al Nat Genet 2010 |
| rs864745 | *JAZF1* | intron | 7 | 7p15.1 | T | C | 0.50 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs2191349 | *DGKB/TMEM195* | intergenic | 7 | 7p21.2 | T | G | 0.50 | Fasting glucose / T2D / Insulin secretion | Dupuis et al Nat Genet 2010 |
| rs17168486 | *DGKB* | intergenic | 7 | 7p21.2 | T | C | 0.19 | T2D | Morris, naturegenetics 2012 |
| rs6467136 | *GCC1-PAX4* | intergenic | 7 | 7q32.1 | G | A | 0.50 (0.81) | Asian T2D | Cho natgen 2012 |
| rs516946 | *ANK1* | intron | 8 | 8p11.21 | C | T | 0.76 | T2D | Morris, naturegenetics 2012 |
| rs896854 | *TP53INP1* | intron | 8 | 8q22.1 | T | C | 0.48 | T2D | Voight et al DIAGRAM2 2010 |
| rs13266634 | *SLC30A8* | coding - missense | 8 | 8q24.11 | C | T | 0.70 | T2D | Sladek R Nature 2007 |
| rs10811661 | *CDKN2B* | intergenic | 9 | 9p21.3 | T | C | 0.80 | T2D | DGI, MIT and LU, Science 2007, Gupta, Diabetologia 2012, Wu Y, Diabetes 2008 |
| rs13292136 | *TLE4 (CHCHD9)* | intergenic | 9 | 9q21.31 | C | T | 0.93 | T2D | Voight et al DIAGRAM2 2010 |
| rs2796441 | *TLE1* | intergenic | 9 | 9q21.32 | G | A | 0.57 | T2D | Morris, naturegenetics 2012 |
| rs7034200 | *GLIS3* | intron | 9 | 9q24.2 | A | C | 0.50 | Fasting glucose /T2D/proinsulin to insulin / insulin secretion | Dupuis et al Nat Genet 2010 |
| rs12779790 | *CDC123,CAMK1D* | intergenic | 10 | 10p13 | G | A | 0.18 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs12571751* | *ZMIZ1* | intron | 10 | 10q22.3 | A | G | 0.52 | T2D / GDM | Morris, naturegenetics 2012 |
| rs1111875* | *HHEX/IDE* | intergenic | 10 | 10q23.33 | C | T | 0.52 | T2D / GDM | DGI, MIT and LU, Science 2007 |

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|---|---|---|---|---|---|---|---|---|---|
| rs7903146 | *TCF7L2* | intronic / promoter | 10 | 10q25.2 | T | C | 0.50 | T2D | Grant SFA, Nat genetics 2006, |
| rs553668 | *ADRA2A* | UTR-3 | 10 | 10q25.2 | A | G | 0.50 | T2D | Rosengren Science 2009 |
| rs10885122 | *ADRA2A* | intergenic | 10 | 10q25.2 | G | T | 0.90 | Fasting glucose / T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs7944584 | *MADD* | intron | 11 | 11p11.2 | A | T | 0.75 | Fasting proinsulin / T2D / Fasting glucose / HOMA B | Dupuis et al Nat Genet 2010 |
| rs5219 | *KCNJ11* | coding - missense | 11 | 11p15.1 | T | C | 0.46 | T2D | DGI, MIT and LU, Science 2007 |
| rs2237895* | *KCNQ1* | intron | 11 | 11p15.4 | C | T | 0.33 | T2D / GDM | Yasuda natgen 2008 |
| rs163184 | *KCNQ1* | intron | 11 | 11p15.4 | G | T | 0.51 | T2D | Yasuda natgen 2008; Morris natgen, 2012 |
| rs2237892 | *KCNQ1* | intron | 11 | 11p15.4 | C | T | 0.69 | T2D | Yasuda Natgen 2008 |
| rs231362 | *KCNQ1* | intron | 11 | 11p15.5 | G | A | 0.52 | Fasting glucose / T2D | Voight et al DIAGRAM2 2010 |
| rs174550 | *FADS1* | intron | 11 | 11q12.2 | T | C | 0.63 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs1552224 | *CENTD2* | intergenic | 11 | 11q13.4 | A | C | 0.88 | T2D | Voight et al DIAGRAM2 2010 |
| rs10830963 | *MTNR1B* | intron | 11 | 11q14.3 | G | C | 0.30 | T2D / Fasting glucose / HOMA B | Prokopenko natgen 2008 |
| rs10842994 | *KLHDC5* | intergenic | 12 | 12p11.22 | C | T | 0.80 | T2D | Morris, naturegenetics 2012 |
| rs11063069 | *CCND2* | intergenic | 12 | 12p13.32 | G | A | 0.21 | T2D | Morris, naturegenetics 2012 |
| rs1153188 | *DCD* | intergenic | 12 | 12q13.2 | A | T | 0.73 | T2D | Zeggini et al Nat Gen 2009 |
| rs1531343 | *HMGA2* | intron of pseudogene | 12 | 12q14.3 | C | G | 0.10 | T2D | Voight et al DIAGRAM2 2010 |
| rs7961581 | *TSPAN8,LGR5* | intergenic | 12 | 12q21.1 | C | T | 0.27 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs35767 | *IGF1* | nearGene-5 | 12 | 12q23.2 | G | A | 0.88 | Fasting glucose/Fasting insulin/T2D / Insulin sensitivity | Dupuis et al Nat Genet 2010 |
| rs7957197 | *OASL/TCF1/HNF1A* | intron of OASL | 12 | 12q24.31 | T | A | 0.85 | T2D | Voight et al DIAGRAM2 2010 |
| rs11071657 | *FAM148B* | intergenic | 15 | 15q22.2 | A | G | 0.77 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs17271305 | *VPS13C* | intron | 15 | 15q22.2 | G | A | 0.42 | 2hr glucose | Saxena et al. Nat Genet 2010 |
| rs7177055* | *HMG20A* | intergenic | 15 | 15q24.3 | A | G | 0.68 | T2D / GDM | Morris, naturegenetics 2012 |
| rs11634397 | *ZFAND6* | intergenic | 15 | 15q25.1 | G | A | 0.60 | T2D | Voight et al DIAGRAM2 2010 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| rs8042680 | *PRC1* | intron | 15 | 15q26.1 | A | C | 0.22 | T2D | Voight et al DIAGRAM2 2010 |
| rs7202877 | *BCAR1* | intergenic | 16 | 16q23.1 | T | G | 0.89 | T2D | Morris, naturegenetics 2012 |
| rs8090011* | *LAMA1* | intron | 18 | 18p11.31 | G | C | 0.36 | T2D / GDM | Perry plos genetics 2012 |
| rs12970134 | *MC4R* | intergenic | 18 | 18q21.32 | A | G | 0.27 | T2D / BMI / waist circumference / insulin resistance | Chambers natgen 2008; Morris, naturegenetics 2012 |
| rs10401969 | *SUGP1* | intron | 19 | 19p13.3 | C | T | 0.08 | T2D | Morris, naturegenetics 2012 |
| rs10423928 | *GIPR* | intron | 19 | 19q13.32 | A | T | 0.17 | 2hr glucose / T2D | Saxena et al. Nat Genet 2010 |
| rs8108269 | *GIPR* | intergenic | 19 | 19q13.32 | G | T | 0.31 | T2D | Morris, naturegenetics 2012 |
| rs6017317 | *FITM2-R3HDML-HNF4A* | intergenic | 20 | 20q13.12 | G | T | 0.18 (0.54) | Asian T2D | Cho natgen 2012 |
| rs5945326* | *DUSP9* | intergenic | X | Xq28 | A | G | 0.79 | T2D / GDM | Voight et al DIAGRAM2 2010 |
| rs11605924* | *CRY2* | intron | 11 | 11p11.2 | A | C | 1.04 | T2D | Dupuis et al Nat Genet 2010 |
| rs9939609 | *FTO* | intron | 16 | 16q12.2 | A | T | 1.20 | T2D, obesity | Frayling et al Nat Genet 2007 |
| rs17133918 | *GRB10* | intron | 7 | 7p12.1 | C | T | | T2D | Prokopenko plos genetics 2013 |
| rs933360 | *GRB10* | intron | 7 | 7p12.1 | A | G | | T2D | Prokopenko plos genetics 2013 |
| rs6943153 | *GRB10* | intron | 7 | 7p12.1 | C | T | 0.0154 (beta) | fasting glucose /fasting insulin | Prokopenko plos genetics 2013 |
| rs7178572* | *HMG20A* | Intergenic | 15 | 7p12.1 | G | A | 1.09 | T2D / GDM | Perry plos genetics 2012; Kooner natgen 2012 |

**Supplementary Table 2a:**
Association of previously reported GDM loci with glycemic traits

| | | | | | | | | Gene |
|---|---|---|---|---|---|---|---|---|
| **depvar** | **genotype** | **beta** | **se** | **lower** | **upper** | **p** | **n** | **Locus** |
| LN_FBS_mmol | rs9939609_A | 0.000 | 0.004 | -0.008 | 0.008 | 0.939 | 3118 | *FTO* |
| LN_PPBS_mmol_ven | rs9939609_A | 0.000 | 0.005 | -0.011 | 0.010 | 0.926 | 3120 | |
| LN_PINS_pmol | rs9939609_A | -0.017 | 0.016 | -0.049 | 0.015 | 0.290 | 3120 | |
| LN_homa2_b_ss | rs9939609_A | -0.005 | 0.012 | -0.029 | 0.019 | 0.688 | 2856 | |
| LN_homa2_ir_ss | rs9939609_A | -0.018 | 0.013 | -0.044 | 0.009 | 0.186 | 2856 | |
| LN_FBS_mmol | rs2796441_G | 0.004 | 0.004 | -0.003 | 0.011 | 0.270 | 3903 | *TLE1* |
| LN_PPBS_mmol_ven | rs2796441_G | -0.001 | 0.005 | -0.010 | 0.008 | 0.799 | 3905 | |
| LN_PINS_pmol | rs2796441_G | -0.016 | 0.014 | -0.043 | 0.012 | 0.268 | 3905 | |
| LN_homa2_b_ss | rs2796441_G | -0.026 | 0.011 | -0.047 | -0.005 | 0.014 | 3577 | |
| LN_homa2_ir_ss | rs2796441_G | -0.023 | 0.012 | -0.046 | 0.000 | 0.050 | 3577 | |
| LN_FBS_mmol | rs560887_C | 0.006 | 0.005 | -0.005 | 0.016 | 0.283 | 3908 | *G6PC2/ABCB11* |
| LN_PPBS_mmol_ven | rs560887_C | 0.003 | 0.007 | -0.010 | 0.016 | 0.647 | 3910 | |
| LN_PINS_pmol | rs560887_C | -0.008 | 0.021 | -0.049 | 0.033 | 0.708 | 3910 | |
| LN_homa2_b_ss | rs560887_C | -0.004 | 0.016 | -0.034 | 0.027 | 0.818 | 3578 | |
| LN_homa2_ir_ss | rs560887_C | 0.017 | 0.017 | -0.017 | 0.051 | 0.323 | 3578 | |
| LN_FBS_mmol | rs11708067_A | -0.008 | 0.004 | -0.016 | 0.000 | 0.055 | 3875 | *ADCY5* |
| LN_PPBS_mmol_ven | rs11708067_A | -0.006 | 0.005 | -0.017 | 0.004 | 0.252 | 3877 | |
| LN_PINS_pmol | rs11708067_A | 0.013 | 0.017 | -0.020 | 0.045 | 0.437 | 3877 | |
| LN_homa2_b_ss | rs11708067_A | 0.024 | 0.012 | 0.000 | 0.049 | 0.053 | 3556 | |
| LN_homa2_ir_ss | rs11708067_A | 0.010 | 0.014 | -0.017 | 0.037 | 0.466 | 3556 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LN_FBS_mmol | rs7754840_C | -0.001 | 0.004 | -0.008 | 0.007 | 0.847 | 3719 | *CDKAL1* |
| LN_PPBS_mmol_ven | rs7754840_C | -0.003 | 0.005 | -0.013 | 0.007 | 0.506 | 3721 | |
| LN_PINS_pmol | rs7754840_C | 0.022 | 0.016 | -0.009 | 0.053 | 0.164 | 3721 | |
| LN_homa2_b_ss | rs7754840_C | 0.012 | 0.012 | -0.011 | 0.036 | 0.295 | 3402 | |
| LN_homa2_ir_ss | rs7754840_C | 0.015 | 0.013 | -0.011 | 0.041 | 0.260 | 3402 | |
| LN_FBS_mmol | rs1111875_C | 0.004 | 0.004 | -0.002 | 0.011 | 0.210 | 3899 | *HHEX* |
| LN_PPBS_mmol_ven | rs1111875_C | 0.005 | 0.005 | -0.004 | 0.014 | 0.258 | 3901 | |
| LN_PINS_pmol | rs1111875_C | -0.008 | 0.014 | -0.035 | 0.019 | 0.567 | 3901 | |
| LN_homa2_b_ss | rs1111875_C | -0.011 | 0.011 | -0.032 | 0.009 | 0.283 | 3572 | |
| LN_homa2_ir_ss | rs1111875_C | -0.005 | 0.012 | -0.028 | 0.018 | 0.688 | 3572 | |
| LN_FBS_mmol | rs7756992_G | -0.002 | 0.004 | -0.010 | 0.006 | 0.609 | 3684 | *CDKAL1* |
| LN_PPBS_mmol_ven | rs7756992_G | -0.002 | 0.005 | -0.012 | 0.008 | 0.754 | 3686 | |
| LN_PINS_pmol | rs7756992_G | 0.004 | 0.016 | -0.027 | 0.036 | 0.778 | 3686 | |
| LN_homa2_b_ss | rs7756992_G | 0.007 | 0.012 | -0.017 | 0.030 | 0.571 | 3372 | |
| LN_homa2_ir_ss | rs7756992_G | 0.000 | 0.013 | -0.026 | 0.026 | 0.990 | 3372 | |
| LN_FBS_mmol | rs10811661_T | 0.002 | 0.005 | -0.008 | 0.012 | 0.757 | 3888 | *CDKN2A/2B* |
| LN_PPBS_mmol_ven | rs10811661_T | -0.003 | 0.007 | -0.016 | 0.010 | 0.661 | 3890 | |
| LN_PINS_pmol | rs10811661_T | -0.008 | 0.020 | -0.048 | 0.032 | 0.697 | 3890 | |
| LN_homa2_b_ss | rs10811661_T | 0.003 | 0.015 | -0.027 | 0.034 | 0.825 | 3561 | |
| LN_homa2_ir_ss | rs10811661_T | -0.003 | 0.017 | -0.037 | 0.030 | 0.856 | 3561 | |
| LN_FBS_mmol | rs4402960_T | -0.004 | 0.003 | -0.010 | 0.003 | 0.311 | 3748 | *IGF2BP2* |
| LN_PPBS_mmol_ven | rs4402960_T | 0.007 | 0.005 | -0.002 | 0.016 | 0.116 | 3750 | |
| LN_PINS_pmol | rs4402960_T | -0.007 | 0.014 | -0.034 | 0.021 | 0.636 | 3750 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LN_homa2_b_ss | rs4402960_T | 0.003 | 0.011 | -0.018 | 0.024 | 0.778 | 3439 | |
| LN_homa2_ir_ss | rs4402960_T | -0.012 | 0.012 | -0.035 | 0.011 | 0.304 | 3439 | |
| LN_FBS_mmol | rs13266634_C | -0.004 | 0.004 | -0.012 | 0.004 | 0.360 | 3896 | *SLC30A8* |
| LN_PPBS_mmol_ven | rs13266634_C | -0.001 | 0.005 | -0.012 | 0.009 | 0.814 | 3898 | |
| LN_PINS_pmol | rs13266634_C | -0.014 | 0.016 | -0.046 | 0.017 | 0.371 | 3898 | |
| LN_homa2_b_ss | rs13266634_C | -0.005 | 0.012 | -0.029 | 0.019 | 0.692 | 3571 | |
| LN_homa2_ir_ss | rs13266634_C | -0.012 | 0.014 | -0.038 | 0.015 | 0.386 | 3571 | |
| LN_FBS_mmol | rs10010131_G | 0.002 | 0.004 | -0.006 | 0.009 | 0.631 | 3841 | *WFS1* |
| LN_PPBS_mmol_ven | rs10010131_G | 0.006 | 0.005 | -0.004 | 0.016 | 0.234 | 3843 | |
| LN_PINS_pmol | rs10010131_G | -0.001 | 0.015 | -0.031 | 0.029 | 0.937 | 3843 | |
| LN_homa2_b_ss | rs10010131_G | -0.004 | 0.011 | -0.027 | 0.018 | 0.718 | 3521 | |
| LN_homa2_ir_ss | rs10010131_G | 0.002 | 0.013 | -0.023 | 0.027 | 0.877 | 3521 | |
| LN_FBS_mmol | rs5219_T | -0.002 | 0.004 | -0.009 | 0.005 | 0.639 | 3593 | *KCNJ11* |
| LN_PPBS_mmol_ven | rs5219_T | 0.008 | 0.005 | -0.001 | 0.018 | 0.075 | 3595 | |
| LN_PINS_pmol | rs5219_T | 0.011 | 0.014 | -0.017 | 0.039 | 0.446 | 3595 | |
| LN_homa2_b_ss | rs5219_T | 0.007 | 0.011 | -0.014 | 0.028 | 0.534 | 3306 | |
| LN_homa2_ir_ss | rs5219_T | 0.001 | 0.012 | -0.023 | 0.024 | 0.940 | 3306 | |

**Supplementary table 3.**
Association of previously reported GDM loci with risk of GDM in Punjabi women based on different glucose cut-offs

Previously reported GDM loci risk allales

| criteria | SNP | Chr | locus | location | effect allele | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs9939609 | 16 | *FTO* | intron | A | 0.001 | 0.058 | 0.985 | 3120 | 982 |
| FBS 7.0 | rs9939609 | 16 | *FTO* | intron | A | 0.179 | 0.266 | 0.502 | 3120 | 30 |
| 2 hr 7.8 | rs9939609 | 16 | *FTO* | intron | A | 0.027 | 0.104 | 0.794 | 3120 | 219 |
| 2 hr 8.5 | rs9939609 | 16 | *FTO* | intron | A | -0.173 | 0.140 | 0.218 | 3120 | 127 |
| FBS 5.1 and PPBS 8.5 | rs9939609 | 16 | *FTO* | intron | A | -0.179 | 0.191 | 0.349 | 3120 | 68 |
| FBS 7.0 and PPBS 7.8 | rs9939609 | 16 | *FTO* | intron | A | 0.113 | 0.322 | 0.726 | 3120 | 21 |

| criteria | genotype | | *locus* | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs2796441 | 9 | *TLE 1* | intergenic | G | 0.070 | 0.049 | 0.153 | 3905 | 1264 |
| FBS 7.0 | rs2796441 | 9 | *TLE 1* | intergenic | G | -0.001 | 0.219 | 0.997 | 3905 | 43 |
| 2 hr 7.8 | rs2796441 | 9 | *TLE 1* | intergenic | G | -0.006 | 0.083 | 0.945 | 3905 | 320 |
| 2 hr 8.5 | rs2796441 | 9 | *TLE 1* | intergenic | G | -0.002 | 0.112 | 0.987 | 3905 | 172 |
| FBS 5.1 and PPBS 8.5 | rs2796441 | 9 | *TLE 1* | intergenic | G | -0.017 | 0.147 | 0.908 | 3905 | 97 |
| FBS 7.0 and PPBS 7.8 | rs2796441 | 9 | *TLE 1* | intergenic | G | 0.023 | 0.276 | 0.933 | 3905 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | 0.110 | 0.074 | 0.134 | 3910 | 1273 |
| FBS 7.0 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | 0.809 | 0.457 | 0.077 | 3910 | 43 |
| 2 hr 7.8 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | 0.126 | 0.129 | 0.329 | 3910 | 322 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 hr 8.5 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | -0.076 | 0.161 | 0.639 | 3910 | 172 |
| FBS 5.1 and PPBS 8.5 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | -0.139 | 0.207 | 0.503 | 3910 | 97 |
| FBS 7.0 and PPBS 7.8 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | 0.563 | 0.511 | 0.271 | 3910 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs11708067 | 3 | *ADCY5* | intron | A | -0.102 | 0.058 | 0.077 | 3877 | 1266 |
| FBS 7.0 | rs11708067 | 3 | *ADCY5* | intron | A | -0.068 | 0.257 | 0.792 | 3877 | 42 |
| 2 hr 7.8 | rs11708067 | 3 | *ADCY5* | intron | A | -0.049 | 0.097 | 0.618 | 3877 | 320 |
| 2 hr 8.5 | rs11708067 | 3 | *ADCY5* | intron | A | -0.111 | 0.129 | 0.390 | 3877 | 171 |
| FBS 5.1 and PPBS 8.5 | rs11708067 | 3 | *ADCY5* | intron | A | -0.005 | 0.175 | 0.978 | 3877 | 95 |
| FBS 7.0 and PPBS 7.8 | rs11708067 | 3 | *ADCY5* | intron | A | -0.413 | 0.301 | 0.169 | 3877 | 26 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.044 | 0.055 | 0.426 | 3721 | 1214 |
| FBS 7.0 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.531 | 0.285 | 0.062 | 3721 | 41 |
| 2 hr 7.8 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.106 | 0.095 | 0.267 | 3721 | 307 |
| 2 hr 8.5 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.066 | 0.127 | 0.602 | 3721 | 163 |
| FBS 5.1 and PPBS 8.5 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.194 | 0.173 | 0.263 | 3721 | 92 |
| FBS 7.0 and PPBS 7.8 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.469 | 0.350 | 0.181 | 3721 | 26 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs1111875 | 10 | *HHEX* | intergenic | C | 0.043 | 0.049 | 0.377 | 3901 | 1265 |
| FBS 7.0 | rs1111875 | 10 | *HHEX* | intergenic | C | -0.185 | 0.223 | 0.406 | 3901 | 43 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2 hr 7.8 | rs1111875 | 10 | *HHEX* | intergenic | C | -0.082 | 0.084 | 0.331 | 3901 | 316 |
| 2 hr 8.5 | rs1111875 | 10 | *HHEX* | intergenic | C | 0.071 | 0.112 | 0.525 | 3901 | 170 |
| FBS 5.1 and PPBS 8.5 | rs1111875 | 10 | *HHEX* | intergenic | C | -0.007 | 0.147 | 0.962 | 3901 | 97 |
| FBS 7.0 and PPBS 7.8 | rs1111875 | 10 | *HHEX* | intergenic | C | -0.055 | 0.278 | 0.843 | 3901 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.042 | 0.056 | 0.450 | 3686 | 1205 |
| FBS 7.0 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.342 | 0.271 | 0.207 | 3686 | 41 |
| 2 hr 7.8 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.067 | 0.095 | 0.484 | 3686 | 305 |
| 2 hr 8.5 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.055 | 0.128 | 0.665 | 3686 | 163 |
| FBS 5.1 and PPBS 8.5 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.254 | 0.177 | 0.152 | 3686 | 92 |
| FBS 7.0 and PPBS 7.8 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.202 | 0.327 | 0.537 | 3686 | 26 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.080 | 0.072 | 0.271 | 3890 | 1259 |
| FBS 7.0 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.240 | 0.351 | 0.494 | 3890 | 43 |
| 2 hr 7.8 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | -0.027 | 0.121 | 0.821 | 3890 | 316 |
| 2 hr 8.5 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.088 | 0.168 | 0.603 | 3890 | 170 |
| FBS 5.1 and PPBS 8.5 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.079 | 0.222 | 0.724 | 3890 | 95 |
| FBS 7.0 and PPBS 7.8 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.169 | 0.430 | 0.694 | 3890 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs4402960 | 3 | *IGF2BP2* | intron | T | -0.062 | 0.049 | 0.208 | 3750 | 1210 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 7.0 | rs4402960 | 3 | *IGF2BP2* | intron | T | -0.324 | 0.224 | 0.149 | 3750 | 43 |
| 2 hr 7.8 | rs4402960 | 3 | *IGF2BP2* | intron | T | 0.048 | 0.083 | 0.563 | 3750 | 307 |
| 2 hr 8.5 | rs4402960 | 3 | *IGF2BP2* | intron | T | 0.004 | 0.111 | 0.968 | 3750 | 168 |
| FBS 5.1 and PPBS 8.5 | rs4402960 | 3 | *IGF2BP2* | intron | T | -0.077 | 0.148 | 0.605 | 3750 | 93 |
| FBS 7.0 and PPBS 7.8 | rs4402960 | 3 | *IGF2BP2* | intron | T | -0.257 | 0.280 | 0.358 | 3750 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.023 | 0.056 | 0.678 | 3898 | 1263 |
| FBS 7.0 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.091 | 0.246 | 0.713 | 3898 | 43 |
| 2 hr 7.8 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.047 | 0.095 | 0.623 | 3898 | 319 |
| 2 hr 8.5 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.020 | 0.128 | 0.873 | 3898 | 171 |
| FBS 5.1 and PPBS 8.5 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | 0.013 | 0.171 | 0.937 | 3898 | 96 |
| FBS 7.0 and PPBS 7.8 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.275 | 0.296 | 0.353 | 3898 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs10010131 | 4 | *WFS 1* | intron | G | 0.005 | 0.053 | 0.928 | 3843 | 1257 |
| FBS 7.0 | rs10010131 | 4 | *WFS 1* | intron | G | 0.352 | 0.262 | 0.180 | 3843 | 41 |
| 2 hr 7.8 | rs10010131 | 4 | *WFS 1* | intron | G | 0.113 | 0.093 | 0.222 | 3843 | 315 |
| 2 hr 8.5 | rs10010131 | 4 | *WFS 1* | intron | G | 0.104 | 0.124 | 0.402 | 3843 | 168 |
| FBS 5.1 and PPBS 8.5 | rs10010131 | 4 | *WFS 1* | intron | G | 0.239 | 0.170 | 0.160 | 3843 | 93 |
| FBS 7.0 and PPBS 7.8 | rs10010131 | 4 | *WFS 1* | intron | G | 0.311 | 0.331 | 0.347 | 3843 | 25 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs5219 | 11 | *KCNJ11* | coding-missense | T | -0.010 | 0.051 | 0.848 | 3595 | 1179 |
| FBS 7.0 | rs5219 | 11 | *KCNJ11* | coding-missense | T | 0.242 | 0.221 | 0.272 | 3595 | 40 |
| 2 hr 7.8 | rs5219 | 11 | *KCNJ11* | coding-missense | T | 0.162 | 0.084 | 0.055 | 3595 | 301 |
| 2 hr 8.5 | rs5219 | 11 | *KCNJ11* | coding-missense | T | 0.109 | 0.114 | 0.335 | 3595 | 160 |
| FBS 5.1 and PPBS 8.5 | rs5219 | 11 | *KCNJ11* | coding-missense | T | 0.105 | 0.151 | 0.486 | 3595 | 89 |
| FBS 7.0 and PPBS 7.8 | rs5219 | 11 | *KCNJ11* | coding-missense | T | -0.039 | 0.286 | 0.892 | 3595 | 25 |

**Supplementary table 4.**
Association of GDM loci with glycemic traitss

| depvar | genotype | beta | se | lower | upper | p | n |
|---|---|---|---|---|---|---|---|
| LN_FBS_mmol | rs13389219_C | 0.002 | 0.004 | -0.005 | 0.010 | 0.575 | 3827 |
| LN_PPBS_mmol_ven | rs13389219_C | 0.009 | 0.005 | -0.001 | 0.019 | 0.074 | 3829 |
| LN_PINS_pmol | rs13389219_C | 0.026 | 0.016 | -0.004 | 0.057 | 0.091 | 3829 |
| LN_homa2_b_ss | rs13389219_C | 0.014 | 0.012 | -0.009 | 0.037 | 0.235 | 3518 |
| LN_homa2_ir_ss | rs13389219_C | 0.029 | 0.013 | 0.004 | 0.055 | 0.026 | 3518 |
| LN_FBS_mmol | rs11920090_T | 0.005 | 0.005 | -0.005 | 0.015 | 0.320 | 3605 |
| LN_PPBS_mmol_ven | rs11920090_T | 0.010 | 0.006 | -0.002 | 0.023 | 0.106 | 3606 |
| LN_PINS_pmol | rs11920090_T | 0.021 | 0.020 | -0.019 | 0.060 | 0.304 | 3606 |
| LN_homa2_b_ss | rs11920090_T | -0.014 | 0.015 | -0.043 | 0.016 | 0.361 | 3301 |
| LN_homa2_ir_ss | rs11920090_T | 0.002 | 0.017 | -0.031 | 0.035 | 0.916 | 3301 |
| LN_FBS_mmol | rs11605924_A | 0.003 | 0.003 | -0.003 | 0.010 | 0.316 | 3907 |
| LN_PPBS_mmol_ven | rs11605924_A | -0.009 | 0.004 | -0.018 | 0.000 | 0.039 | 3909 |
| LN_PINS_pmol | rs11605924_A | -0.015 | 0.014 | -0.042 | 0.011 | 0.262 | 3909 |
| LN_homa2_b_ss | rs11605924_A | -0.011 | 0.010 | -0.032 | 0.009 | 0.264 | 3583 |
| LN_homa2_ir_ss | rs11605924_A | -0.013 | 0.011 | -0.035 | 0.009 | 0.247 | 3583 |
| LN_FBS_mmol | rs1552224_A | -0.005 | 0.005 | -0.014 | 0.005 | 0.328 | 3909 |
| LN_PPBS_mmol_ven | rs1552224_A | 0.004 | 0.006 | -0.008 | 0.016 | 0.482 | 3911 |
| LN_PINS_pmol | rs1552224_A | -0.016 | 0.019 | -0.052 | 0.020 | 0.383 | 3911 |
| LN_homa2_b_ss | rs1552224_A | 0.003 | 0.014 | -0.024 | 0.031 | 0.817 | 3579 |
| LN_homa2_ir_ss | rs1552224_A | -0.017 | 0.016 | -0.047 | 0.014 | 0.282 | 3579 |

**Supplementary table 5.**
Association of selected T2D risk loci with risk of GDM in Punjabi women based on different glucose cut-offs

| | | | | FBS = 5,1 | | | | | | FBS = 7,0 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | effect allele | Chr | Locus | n | n_cases | OR | CI(lower) | CI(upper) | pval | n | n_cases | OR | CI(lower) | CI(upper) | pval |
| rs2296172 | G | 1 | *MACF1* | 3847 | 1242 | 1.049 | 0.901 | 1.221 | 0.539 | 3847 | 42 | 0.803 | 0.383 | 1.680 | 0.559 |
| rs340874 | C | 1 | *PROX1* | 3709 | 1212 | 0.970 | 0.881 | 1.068 | 0.534 | 3709 | 40 | 1.059 | 0.684 | 1.640 | 0.797 |
| rs7578597 | T | 2 | *THADA* | 3710 | 1208 | 0.939 | 0.817 | 1.079 | 0.374 | 3710 | 40 | 0.929 | 0.500 | 1.723 | 0.814 |
| rs243088 | T | 2 | *BCL 11A* | 3717 | 1218 | 1.036 | 0.940 | 1.143 | 0.474 | 3717 | 41 | 1.088 | 0.702 | 1.688 | 0.706 |
| rs998451* | A | 2 | *TMEM163* | 3882 | 1268 | 0.949 | 0.833 | 1.081 | 0.431 | 3882 | 42 | 0.848 | 0.455 | 1.583 | 0.606 |
| rs7593730 | T | 2 | *RBMS1/ITGB6* | 3906 | 1268 | 1.012 | 0.901 | 1.135 | 0.846 | 3906 | 42 | 1.212 | 0.737 | 1.994 | 0.449 |
| rs7607980 | C | 2 | *COBL1* | 3885 | 1256 | 0.936 | 0.801 | 1.094 | 0.404 | 3885 | 43 | 0.701 | 0.319 | 1.540 | 0.376 |
| rs13389219 | C | 2 | *GRB14* | 3829 | 1246 | 1.083 | 0.972 | 1.207 | 0.148 | 3829 | 40 | 1.005 | 0.612 | 1.652 | 0.983 |
| rs560887 | C | 2 | *G6PC2/ABCB11* | 3910 | 1273 | 1.117 | 0.966 | 1.291 | 0.134 | 3910 | 43 | 2.246 | 0.917 | 5.501 | 0.077 |
| rs7578326 | A | 2 | *KIAA1486/IRS1* | 3600 | 1170 | 0.966 | 0.859 | 1.085 | 0.556 | 3600 | 40 | 0.961 | 0.574 | 1.610 | 0.881 |
| rs2943641 | C | 2 | *IRS1* | 3643 | 1191 | 0.972 | 0.868 | 1.087 | 0.616 | 3643 | 39 | 0.866 | 0.528 | 1.419 | 0.568 |
| rs4675095 | A | 2 | *IRS1* | 3817 | 1250 | 1.017 | 0.883 | 1.172 | 0.814 | 3817 | 40 | 0.869 | 0.469 | 1.609 | 0.655 |
| rs1801282 | C | 3 | *PPARG* | 3652 | 1196 | 0.999 | 0.864 | 1.155 | 0.993 | 3652 | 41 | 0.679 | 0.386 | 1.195 | 0.180 |
| rs831571 | C | 3 | *PSMD6* | 3726 | 1216 | 0.932 | 0.828 | 1.049 | 0.245 | 3726 | 41 | 0.970 | 0.571 | 1.647 | 0.910 |
| rs4607103 | C | 3 | *ADAMTS9-AS2* | 3884 | 1257 | 1.002 | 0.912 | 1.102 | 0.962 | 3884 | 43 | 1.336 | 0.874 | 2.042 | 0.181 |
| rs11708067 | A | 3 | *ADCY5* | 3877 | 1266 | 0.903 | 0.807 | 1.011 | 0.077 | 3877 | 42 | 0.934 | 0.565 | 1.546 | 0.792 |
| rs11920090 | T | 3 | *SLC2A2* | 3606 | 1172 | 1.146 | 0.998 | 1.316 | 0.053 | 3606 | 40 | 2.076 | 0.947 | 4.548 | 0.068 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs4402960 | T | 3 | *IGF2BP2* | 3750 | 1210 | 0.940 | 0.853 | 1.035 | 0.208 | 3750 | 43 | 0.723 | 0.466 | 1.123 | 0.149 |
| rs6815464 | C | 4 | *MAEA* | 3722 | 1218 | 1.061 | 0.926 | 1.214 | 0.394 | 3722 | 41 | 1.502 | 0.751 | 3.005 | 0.250 |
| rs10010131 | G | 4 | *WFS1* | 3843 | 1257 | 1.005 | 0.905 | 1.115 | 0.928 | 3843 | 41 | 1.422 | 0.850 | 2.377 | 0.180 |
| rs459193 | G | 5 | *ANKRD55* | 3884 | 1269 | 1.053 | 0.954 | 1.163 | 0.306 | 3884 | 42 | 0.643 | 0.417 | 0.990 | 0.045 |
| rs4457053 | G | 5 | *ZBED3* | 3579 | 1165 | 0.941 | 0.833 | 1.062 | 0.324 | 3579 | 40 | 0.996 | 0.582 | 1.704 | 0.987 |
| rs7754840 | C | 6 | *CDKAL 1* | 3721 | 1214 | 0.957 | 0.859 | 1.066 | 0.426 | 3721 | 41 | 0.588 | 0.336 | 1.028 | 0.062 |
| rs7756992 | G | 6 | *CDKAL 1* | 3686 | 1205 | 0.959 | 0.860 | 1.069 | 0.450 | 3686 | 41 | 0.711 | 0.418 | 1.208 | 0.207 |
| rs9470794 | C | 6 | *ZFAND3* | 3608 | 1173 | 1.054 | 0.910 | 1.221 | 0.481 | 3608 | 40 | 0.999 | 0.518 | 1.929 | 0.998 |
| rs17168486 | T | 7 | *DGKB* | 3855 | 1249 | 0.983 | 0.887 | 1.090 | 0.749 | 3855 | 43 | 0.621 | 0.372 | 1.039 | 0.070 |
| rs2191349 | T | 7 | *DGKB/TMEM195* | 3903 | 1262 | 0.990 | 0.899 | 1.091 | 0.845 | 3903 | 43 | 1.283 | 0.818 | 2.012 | 0.278 |
| rs864745 | T | 7 | *JAZF1* | 3876 | 1260 | 1.021 | 0.919 | 1.134 | 0.700 | 3876 | 43 | 0.808 | 0.518 | 1.263 | 0.350 |
| rs4607517 | A | 7 | *GCK* | 3903 | 1271 | 1.027 | 0.892 | 1.183 | 0.710 | 3903 | 43 | 0.976 | 0.514 | 1.851 | 0.940 |
| rs17133918 | T | 7 | *GRB10* | 3907 | 1265 | 0.991 | 0.892 | 1.101 | 0.868 | 3907 | 43 | 1.268 | 0.812 | 1.980 | 0.297 |
| rs933360 | A | 7 | *GRB10* | 3905 | 1272 | 1.021 | 0.924 | 1.128 | 0.687 | 3905 | 43 | 1.207 | 0.758 | 1.920 | 0.428 |
| rs6943153 | T | 7 | *GRB10* | 3602 | 1174 | 0.972 | 0.876 | 1.079 | 0.594 | 3602 | 40 | 0.901 | 0.562 | 1.443 | 0.664 |
| rs1799999* | A | 7 | *PP1R3A* | 3890 | 1270 | 0.991 | 0.898 | 1.094 | 0.860 | 3890 | 43 | 0.820 | 0.521 | 1.288 | 0.388 |
| rs6467136 | G | 7 | *GCC1-PAX4* | 3593 | 1163 | 0.954 | 0.868 | 1.048 | 0.329 | 3593 | 39 | 1.912 | 1.168 | 3.128 | 0.010 |
| rs516946 | C | 8 | *ANK1* | 3922 | 1273 | 1.115 | 0.988 | 1.258 | 0.078 | 3922 | 43 | 0.961 | 0.566 | 1.632 | 0.883 |
| rs896854 | T | 8 | *TP53INP1* | 3903 | 1274 | 0.980 | 0.891 | 1.079 | 0.685 | 3903 | 42 | 1.295 | 0.845 | 1.985 | 0.235 |
| rs13266634 | C | 8 | *SLC30A8* | 3898 | 1263 | 0.977 | 0.875 | 1.091 | 0.678 | 3898 | 43 | 0.913 | 0.564 | 1.479 | 0.713 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs7034200 | A | 9 | *GLIS3* | 3868 | 1250 | 1.032 | 0.938 | 1.135 | 0.515 | 3868 | 43 | 1.113 | 0.729 | 1.700 | 0.619 |
| rs10811661 | T | 9 | *CDKN2A/2B* | 3890 | 1259 | 1.083 | 0.940 | 1.248 | 0.271 | 3890 | 43 | 1.271 | 0.639 | 2.527 | 0.494 |
| rs13292136 | C | 9 | *TLE4 (CHCHD9)* | 3706 | 1214 | 0.991 | 0.866 | 1.133 | 0.891 | 3706 | 41 | 0.924 | 0.514 | 1.663 | 0.793 |
| rs2796441 | G | 9 | *TLE 1* | 3905 | 1264 | 1.073 | 0.974 | 1.181 | 0.153 | 3905 | 43 | 0.999 | 0.650 | 1.536 | 0.997 |
| rs12571751 | A | 10 | *ZMIZ1* | 3601 | 1173 | 0.974 | 0.880 | 1.077 | 0.601 | 3601 | 40 | 0.882 | 0.564 | 1.379 | 0.582 |
| rs1111875 | C | 10 | *HHEX* | 3901 | 1265 | 1.044 | 0.949 | 1.150 | 0.377 | 3901 | 43 | 0.831 | 0.537 | 1.286 | 0.406 |
| rs553668 | A | 10 | *ADRA2A* | 3666 | 1197 | 1.058 | 0.953 | 1.175 | 0.293 | 3666 | 39 | 1.024 | 0.636 | 1.651 | 0.921 |
| rs10885122 | G | 10 | *ADRA2A* | 3683 | 1201 | 1.038 | 0.920 | 1.171 | 0.549 | 3683 | 41 | 1.188 | 0.675 | 2.089 | 0.550 |
| rs7903146 | T | 10 | *TCF7L2* | 3543 | 1164 | 1.007 | 0.905 | 1.121 | 0.892 | 3543 | 38 | 1.154 | 0.718 | 1.853 | 0.555 |
| rs689* | A | 11 | *INS,INS-IGF2* | 3903 | 1267 | 1.043 | 0.920 | 1.182 | 0.514 | 3903 | 43 | 1.381 | 0.827 | 2.307 | 0.217 |
| rs163184 | G | 11 | *KCNQ1* | 3713 | 1215 | 1.002 | 0.907 | 1.107 | 0.967 | 3713 | 43 | 1.056 | 0.683 | 1.634 | 0.805 |
| rs2237895 | C | 11 | *KCNQ1* | 3682 | 1200 | 1.013 | 0.918 | 1.117 | 0.799 | 3682 | 40 | 1.199 | 0.775 | 1.855 | 0.415 |
| rs5219 | T | 11 | *KCNJ11* | 3595 | 1179 | 0.990 | 0.897 | 1.094 | 0.848 | 3595 | 40 | 1.274 | 0.827 | 1.964 | 0.272 |
| rs11605924 | A | 11 | *CRY2* | 3909 | 1275 | 1.039 | 0.947 | 1.141 | 0.417 | 3909 | 42 | 1.147 | 0.752 | 1.750 | 0.524 |
| rs7944584 | A | 11 | *MADD* | 3553 | 1168 | 1.081 | 0.954 | 1.226 | 0.222 | 3553 | 38 | 0.993 | 0.564 | 1.749 | 0.981 |
| rs174550 | T | 11 | *FADS1* | 3908 | 1272 | 0.981 | 0.865 | 1.114 | 0.771 | 3908 | 43 | 0.888 | 0.515 | 1.531 | 0.670 |
| rs1552224 | A | 11 | *CENTD2* | 3911 | 1274 | 0.844 | 0.745 | 0.956 | 0.007 | 3911 | 43 | 1.150 | 0.636 | 2.080 | 0.644 |
| rs10830963 | G | 11 | *MTNR1B* | 3714 | 1214 | 0.988 | 0.894 | 1.091 | 0.809 | 3714 | 41 | 0.885 | 0.563 | 1.392 | 0.597 |
| rs11063069 | G | 12 | *CCND2* | 3671 | 1203 | 1.028 | 0.899 | 1.176 | 0.687 | 3671 | 40 | 0.552 | 0.255 | 1.195 | 0.132 |
| rs10842994 | C | 12 | *KLHDC5* | 3906 | 1273 | 0.941 | 0.819 | 1.081 | 0.391 | 3906 | 42 | 0.736 | 0.417 | 1.299 | 0.290 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs1153188 | A | 12 | *DCD* | 3912 | 1275 | 1.018 | 0.900 | 1.151 | 0.777 | 3912 | 43 | 1.249 | 0.691 | 2.258 | 0.461 |
| rs1531343 | C | 12 | *HMGA2* | 3915 | 1270 | 0.904 | 0.799 | 1.023 | 0.109 | 3915 | 42 | 0.739 | 0.400 | 1.363 | 0.332 |
| rs7961581 | C | 12 | *TSPAN8,LGR5* | 3703 | 1211 | 1.028 | 0.928 | 1.139 | 0.601 | 3703 | 41 | 1.074 | 0.682 | 1.691 | 0.758 |
| rs35767 | G | 12 | *IGF1* | 3910 | 1275 | 0.960 | 0.857 | 1.076 | 0.488 | 3910 | 43 | 0.787 | 0.483 | 1.280 | 0.334 |
| rs7957197 | T | 12 | *OASL/TCF1/HNF1A* | 3924 | 1274 | 1.016 | 0.837 | 1.232 | 0.876 | 3924 | 43 | 0.789 | 0.365 | 1.709 | 0.548 |
| rs9552911* | A | 13 | *SGCG* | 3890 | 1271 | 1.045 | 0.897 | 1.218 | 0.569 | 3890 | 43 | 1.237 | 0.656 | 2.332 | 0.511 |
| rs17271305 | G | 15 | *VPS13C* | 3825 | 1249 | 0.910 | 0.819 | 1.011 | 0.078 | 3825 | 42 | 0.883 | 0.545 | 1.431 | 0.613 |
| rs11071657 | A | 15 | *FAM148B* | 3897 | 1264 | 0.917 | 0.827 | 1.016 | 0.096 | 3897 | 43 | 0.896 | 0.571 | 1.405 | 0.632 |
| rs7177055 | A | 15 | *HMG20A* | 3907 | 1268 | 0.951 | 0.865 | 1.046 | 0.304 | 3907 | 43 | 1.040 | 0.679 | 1.593 | 0.857 |
| rs11634397 | G | 15 | *ZFAND6* | 3910 | 1268 | 0.974 | 0.884 | 1.073 | 0.593 | 3910 | 43 | 0.942 | 0.612 | 1.450 | 0.786 |
| rs8042680 | A | 15 | *PRC1* | 3887 | 1259 | 0.990 | 0.897 | 1.093 | 0.844 | 3887 | 43 | 0.959 | 0.616 | 1.491 | 0.851 |
| rs9939609 | A | 16 | *FTO* | 3120 | 982 | 1.001 | 0.894 | 1.121 | 0.985 | 3120 | 30 | 1.196 | 0.710 | 2.014 | 0.502 |
| rs7202877 | T | 16 | *BCAR1* | 3915 | 1275 | 1.059 | 0.884 | 1.269 | 0.534 | 3915 | 43 | 1.577 | 0.587 | 4.242 | 0.366 |
| rs8090011 | G | 18 | *LAMA1* | 3911 | 1267 | 0.934 | 0.849 | 1.027 | 0.160 | 3911 | 43 | 1.181 | 0.771 | 1.809 | 0.444 |
| rs10401969 | C | 19 | *SUGP1* | 3605 | 1172 | 0.830 | 0.700 | 0.983 | 0.031 | 3605 | 40 | 0.591 | 0.238 | 1.467 | 0.257 |
| rs8108269 | G | 19 | *GIPR* | 3508 | 1129 | 1.044 | 0.938 | 1.162 | 0.426 | 3508 | 40 | 1.025 | 0.642 | 1.637 | 0.916 |
| rs10423928 | A | 19 | *GIPR* | 3911 | 1272 | 1.068 | 0.935 | 1.219 | 0.332 | 3911 | 42 | 0.530 | 0.245 | 1.146 | 0.107 |
| rs6017317 | G | 20 | *FITM2-R3HDML-HNF4A* | 3758 | 1224 | 0.968 | 0.875 | 1.072 | 0.535 | 3758 | 42 | 0.906 | 0.575 | 1.429 | 0.672 |
| rs5945326 | A | X | *DUSP9* | 3589 | 1163 | 1.017 | 0.919 | 1.125 | 0.745 | 3589 | 39 | 1.075 | 0.680 | 1.698 | 0.757 |
| rs4812829* | A | 20 | *HNF4A* | 3801 | 1236 | 0.97 | 0.88 | 1.08 | 0.63 | 3801 | 42 | 1.260 | 0.790 | 1.980 | 0.320 |
| rs7178572* | G | 15 | *HMG20A* | 3541 | 1140 | 0.99 | 0.9 | 1.1 | 0.93 | 3541 | 38 | 0.970 | 0.610 | 1.520 | 0.900 |

| | | | | PPBS = 7,8 | | | | | | PPBS = 8,5 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | effect allele | Chr | Locus | n | n_cases | OR | CI(lower) | CI(upper) | pval | n | n_cases | OR | CI(lower) | CI(upper) | pval |
| rs2296172 | G | 1 | *MACF1* | 3847 | 317 | 0.929 | 0.713 | 1.210 | 0.584 | 3847 | 170 | 0.953 | 0.670 | 1.355 | 0.787 |
| rs340874 | C | 1 | *PROX1* | 3709 | 306 | 0.931 | 0.790 | 1.096 | 0.389 | 3709 | 162 | 0.914 | 0.734 | 1.139 | 0.423 |
| rs7578597 | T | 2 | *THADA* | 3710 | 307 | 0.887 | 0.705 | 1.117 | 0.308 | 3710 | 164 | 0.770 | 0.574 | 1.034 | 0.082 |
| rs243088 | T | 2 | *BCL 11A* | 3717 | 308 | 1.090 | 0.923 | 1.287 | 0.311 | 3717 | 165 | 1.203 | 0.963 | 1.503 | 0.103 |
| rs998451* | A | 2 | *TMEM163* | 3882 | 319 | 0.984 | 0.788 | 1.228 | 0.886 | 3882 | 171 | 0.897 | 0.659 | 1.219 | 0.486 |
| rs7593730 | T | 2 | *RBMS1/ITGB6* | 3906 | 322 | 1.003 | 0.824 | 1.220 | 0.978 | 3906 | 172 | 0.919 | 0.702 | 1.202 | 0.537 |
| rs7607980 | C | 2 | *COBL1* | 3885 | 320 | 0.984 | 0.756 | 1.280 | 0.901 | 3885 | 172 | 1.262 | 0.912 | 1.747 | 0.160 |
| rs13389219 | C | 2 | *GRB14* | 3829 | 315 | 1.249 | 1.031 | 1.512 | 0.023 | 3829 | 168 | 1.164 | 0.904 | 1.500 | 0.239 |
| rs560887 | C | 2 | *G6PC2/ABCB11* | 3910 | 322 | 1.134 | 0.881 | 1.460 | 0.329 | 3910 | 172 | 0.927 | 0.676 | 1.272 | 0.639 |
| rs7578326 | A | 2 | *KIAA1486/IRS1* | 3600 | 296 | 0.930 | 0.764 | 1.132 | 0.470 | 3600 | 160 | 0.973 | 0.747 | 1.267 | 0.838 |
| rs2943641 | C | 2 | *IRS1* | 3643 | 298 | 0.901 | 0.746 | 1.089 | 0.281 | 3643 | 160 | 0.906 | 0.704 | 1.165 | 0.441 |
| rs4675095 | A | 2 | *IRS1* | 3817 | 313 | 1.119 | 0.871 | 1.437 | 0.379 | 3817 | 167 | 1.203 | 0.852 | 1.699 | 0.293 |
| rs1801282 | C | 3 | *PPARG* | 3652 | 304 | 0.898 | 0.708 | 1.139 | 0.374 | 3652 | 163 | 1.007 | 0.725 | 1.400 | 0.966 |
| rs831571 | C | 3 | *PSMD6* | 3726 | 309 | 1.060 | 0.864 | 1.300 | 0.579 | 3726 | 165 | 1.212 | 0.911 | 1.611 | 0.186 |
| rs4607103 | C | 3 | *ADAMTS9-AS2* | 3884 | 315 | 1.104 | 0.939 | 1.297 | 0.230 | 3884 | 169 | 1.123 | 0.905 | 1.394 | 0.293 |
| rs11708067 | A | 3 | *ADCY5* | 3877 | 320 | 0.953 | 0.787 | 1.153 | 0.618 | 3877 | 171 | 0.895 | 0.696 | 1.152 | 0.390 |
| rs11920090 | T | 3 | *SLC2A2* | 3606 | 299 | 1.179 | 0.927 | 1.500 | 0.181 | 3606 | 162 | 1.457 | 1.032 | 2.056 | 0.032 |
| rs4402960 | T | 3 | *IGF2BP2* | 3750 | 307 | 1.049 | 0.891 | 1.235 | 0.563 | 3750 | 168 | 1.004 | 0.809 | 1.247 | 0.968 |
| rs6815464 | C | 4 | *MAEA* | 3722 | 307 | 1.036 | 0.822 | 1.305 | 0.767 | 3722 | 165 | 0.924 | 0.685 | 1.246 | 0.605 |
| rs10010131 | G | 4 | *WFS1* | 3843 | 315 | 1.120 | 0.934 | 1.343 | 0.222 | 3843 | 168 | 1.110 | 0.870 | 1.416 | 0.402 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs459193 | G | 5 | *ANKRD55* | 3884 | 318 | 1.007 | 0.850 | 1.192 | 0.940 | 3884 | 169 | 1.066 | 0.848 | 1.340 | 0.585 |
| rs4457053 | G | 5 | *ZBED3* | 3579 | 297 | 1.082 | 0.885 | 1.324 | 0.440 | 3579 | 162 | 1.157 | 0.891 | 1.504 | 0.274 |
| rs7754840 | C | 6 | *CDKAL 1* | 3721 | 307 | 0.900 | 0.746 | 1.084 | 0.267 | 3721 | 163 | 0.936 | 0.729 | 1.201 | 0.602 |
| rs7756992 | G | 6 | *CDKAL 1* | 3686 | 305 | 0.935 | 0.776 | 1.128 | 0.484 | 3686 | 163 | 0.946 | 0.737 | 1.215 | 0.665 |
| rs9470794 | C | 6 | *ZFAND3* | 3608 | 299 | 1.082 | 0.848 | 1.382 | 0.525 | 3608 | 163 | 0.920 | 0.653 | 1.296 | 0.633 |
| rs17168486 | T | 7 | *DGKB* | 3855 | 314 | 0.996 | 0.836 | 1.187 | 0.965 | 3855 | 169 | 0.824 | 0.646 | 1.052 | 0.121 |
| rs2191349 | T | 7 | *DGKB/TMEM195* | 3903 | 320 | 1.074 | 0.909 | 1.268 | 0.404 | 3903 | 172 | 1.138 | 0.909 | 1.425 | 0.259 |
| rs864745 | T | 7 | *JAZF1* | 3876 | 316 | 0.978 | 0.818 | 1.168 | 0.803 | 3876 | 170 | 0.976 | 0.770 | 1.238 | 0.844 |
| rs4607517 | A | 7 | *GCK* | 3903 | 322 | 1.082 | 0.854 | 1.369 | 0.514 | 3903 | 172 | 0.929 | 0.667 | 1.294 | 0.662 |
| rs17133918 | T | 7 | *GRB10* | 3907 | 318 | 1.021 | 0.854 | 1.221 | 0.819 | 3907 | 172 | 1.063 | 0.840 | 1.346 | 0.612 |
| rs933360 | A | 7 | *GRB10* | 3905 | 322 | 1.014 | 0.856 | 1.202 | 0.871 | 3905 | 173 | 1.108 | 0.880 | 1.395 | 0.381 |
| rs6943153 | T | 7 | *GRB10* | 3602 | 298 | 0.880 | 0.735 | 1.053 | 0.161 | 3602 | 163 | 0.775 | 0.608 | 0.989 | 0.040 |
| rs1799999* | A | 7 | *PP1R3A* | 3890 | 320 | 0.851 | 0.718 | 1.009 | 0.063 | 3890 | 173 | 0.850 | 0.677 | 1.067 | 0.161 |
| rs6467136 | G | 7 | *GCC1-PAX4* | 3593 | 303 | 1.115 | 0.949 | 1.310 | 0.184 | 3593 | 162 | 1.253 | 1.006 | 1.561 | 0.044 |
| rs516946 | C | 8 | *ANK1* | 3922 | 325 | 1.038 | 0.847 | 1.273 | 0.717 | 3922 | 173 | 0.993 | 0.758 | 1.300 | 0.957 |
| rs896854 | T | 8 | *TP53INP1* | 3903 | 320 | 0.942 | 0.799 | 1.110 | 0.477 | 3903 | 171 | 0.906 | 0.726 | 1.131 | 0.384 |
| rs13266634 | C | 8 | *SLC30A8* | 3898 | 319 | 0.954 | 0.792 | 1.150 | 0.623 | 3898 | 171 | 0.980 | 0.762 | 1.259 | 0.873 |
| rs7034200 | A | 9 | *GLIS3* | 3868 | 315 | 0.982 | 0.834 | 1.155 | 0.822 | 3868 | 169 | 0.875 | 0.704 | 1.088 | 0.230 |
| rs10811661 | T | 9 | *CDKN2A/2B* | 3890 | 316 | 0.973 | 0.767 | 1.234 | 0.821 | 3890 | 170 | 1.092 | 0.785 | 1.518 | 0.603 |
| rs13292136 | C | 9 | *TLE4 (CHCHD9)* | 3706 | 304 | 0.938 | 0.749 | 1.175 | 0.578 | 3706 | 164 | 0.994 | 0.732 | 1.350 | 0.972 |
| rs2796441 | G | 9 | *TLE 1* | 3905 | 320 | 0.994 | 0.844 | 1.171 | 0.945 | 3905 | 172 | 0.998 | 0.802 | 1.242 | 0.987 |
| rs12571751 | A | 10 | *ZMIZ1* | 3601 | 299 | 0.874 | 0.737 | 1.036 | 0.121 | 3601 | 163 | 0.900 | 0.717 | 1.128 | 0.359 |
| rs1111875 | C | 10 | *HHEX* | 3901 | 316 | 0.921 | 0.781 | 1.087 | 0.331 | 3901 | 170 | 1.074 | 0.862 | 1.337 | 0.525 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs553668 | A | 10 | *ADRA2A* | 3666 | 301 | 1.162 | 0.976 | 1.385 | 0.092 | 3666 | 163 | 1.184 | 0.939 | 1.493 | 0.154 |
| rs10885122 | G | 10 | *ADRA2A* | 3683 | 303 | 1.020 | 0.831 | 1.253 | 0.849 | 3683 | 160 | 1.031 | 0.781 | 1.361 | 0.828 |
| rs7903146 | T | 10 | *TCF7L2* | 3543 | 293 | 1.123 | 0.938 | 1.343 | 0.206 | 3543 | 156 | 1.257 | 0.992 | 1.593 | 0.058 |
| rs689* | A | 11 | *INS,INS-IGF2* | 3903 | 319 | 1.099 | 0.891 | 1.355 | 0.377 | 3903 | 172 | 1.082 | 0.817 | 1.432 | 0.582 |
| rs163184 | G | 11 | *KCNQ1* | 3713 | 307 | 0.897 | 0.758 | 1.061 | 0.204 | 3713 | 165 | 0.888 | 0.710 | 1.112 | 0.300 |
| rs2237895 | C | 11 | *KCNQ1* | 3682 | 304 | 0.959 | 0.812 | 1.133 | 0.623 | 3682 | 161 | 0.895 | 0.714 | 1.122 | 0.337 |
| rs5219 | T | 11 | *KCNJ11* | 3595 | 301 | 1.176 | 0.997 | 1.387 | 0.055 | 3595 | 160 | 1.116 | 0.893 | 1.394 | 0.335 |
| rs11605924 | A | 11 | *CRY2* | 3909 | 318 | 0.832 | 0.709 | 0.976 | 0.024 | 3909 | 169 | 0.785 | 0.632 | 0.974 | 0.028 |
| rs7944584 | A | 11 | *MADD* | 3553 | 294 | 0.909 | 0.739 | 1.117 | 0.364 | 3553 | 157 | 1.049 | 0.787 | 1.399 | 0.743 |
| rs174550 | T | 11 | *FADS1* | 3908 | 322 | 0.975 | 0.787 | 1.208 | 0.819 | 3908 | 172 | 0.920 | 0.694 | 1.219 | 0.561 |
| rs1552224 | A | 11 | *CENTD2* | 3911 | 323 | 0.917 | 0.743 | 1.132 | 0.420 | 3911 | 173 | 0.983 | 0.737 | 1.310 | 0.906 |
| rs10830963 | G | 11 | *MTNR1B* | 3714 | 305 | 0.897 | 0.755 | 1.066 | 0.217 | 3714 | 162 | 0.926 | 0.735 | 1.166 | 0.514 |
| rs11063069 | G | 12 | *CCND2* | 3671 | 305 | 1.000 | 0.795 | 1.258 | 0.998 | 3671 | 164 | 0.846 | 0.612 | 1.171 | 0.314 |
| rs10842994 | C | 12 | *KLHDC5* | 3906 | 321 | 1.163 | 0.904 | 1.495 | 0.240 | 3906 | 171 | 1.070 | 0.771 | 1.486 | 0.685 |
| rs1153188 | A | 12 | *DCD* | 3912 | 323 | 1.179 | 0.947 | 1.467 | 0.141 | 3912 | 173 | 1.010 | 0.763 | 1.337 | 0.942 |
| rs1531343 | C | 12 | *HMGA2* | 3915 | 321 | 0.839 | 0.674 | 1.044 | 0.115 | 3915 | 170 | 0.920 | 0.690 | 1.226 | 0.568 |
| rs7961581 | C | 12 | *TSPAN8,LGR5* | 3703 | 304 | 0.892 | 0.747 | 1.066 | 0.209 | 3703 | 163 | 0.878 | 0.691 | 1.115 | 0.286 |
| rs35767 | G | 12 | *IGF1* | 3910 | 322 | 0.909 | 0.752 | 1.100 | 0.329 | 3910 | 172 | 0.958 | 0.740 | 1.240 | 0.746 |
| rs7957197 | T | 12 | *OASL/TCF1/HNF1A* | 3924 | 325 | 0.852 | 0.627 | 1.157 | 0.304 | 3924 | 173 | 0.958 | 0.624 | 1.471 | 0.845 |
| rs9552911* | A | 13 | *SGCG* | 3890 | 317 | 1.048 | 0.811 | 1.356 | 0.719 | 3890 | 169 | 0.880 | 0.609 | 1.272 | 0.497 |
| rs17271305 | G | 15 | *VPS13C* | 3825 | 317 | 1.031 | 0.864 | 1.230 | 0.735 | 3825 | 169 | 0.969 | 0.763 | 1.231 | 0.794 |
| rs11071657 | A | 15 | *FAM148B* | 3897 | 318 | 1.035 | 0.867 | 1.235 | 0.705 | 3897 | 170 | 1.105 | 0.869 | 1.404 | 0.416 |
| rs7177055 | A | 15 | *HMG20A* | 3907 | 319 | 1.013 | 0.862 | 1.192 | 0.873 | 3907 | 171 | 1.223 | 0.982 | 1.522 | 0.072 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11634397 | G | 15 | *ZFAND6* | 3910 | 321 | 0.881 | 0.748 | 1.038 | 0.129 | 3910 | 170 | 0.919 | 0.737 | 1.145 | 0.451 |
| rs8042680 | A | 15 | *PRC1* | 3887 | 317 | 0.880 | 0.744 | 1.040 | 0.134 | 3887 | 170 | 0.894 | 0.715 | 1.119 | 0.329 |
| rs9939609 | A | 16 | *FTO* | 3120 | 219 | 1.028 | 0.838 | 1.261 | 0.794 | 3120 | 127 | 0.841 | 0.639 | 1.107 | 0.218 |
| rs7202877 | T | 16 | *BCAR1* | 3915 | 322 | 1.181 | 0.854 | 1.635 | 0.315 | 3915 | 173 | 0.918 | 0.620 | 1.359 | 0.669 |
| rs8090011 | G | 18 | *LAMA1* | 3911 | 320 | 0.926 | 0.787 | 1.089 | 0.353 | 3911 | 172 | 0.942 | 0.758 | 1.170 | 0.587 |
| rs10401969 | C | 19 | *SUGP1* | 3605 | 298 | 1.006 | 0.760 | 1.333 | 0.964 | 3605 | 161 | 1.102 | 0.767 | 1.584 | 0.598 |
| rs8108269 | G | 19 | *GIPR* | 3508 | 302 | 1.024 | 0.857 | 1.222 | 0.795 | 3508 | 159 | 1.128 | 0.890 | 1.428 | 0.319 |
| rs10423928 | A | 19 | *GIPR* | 3911 | 321 | 0.898 | 0.711 | 1.136 | 0.370 | 3911 | 171 | 0.863 | 0.626 | 1.188 | 0.366 |
| rs6017317 | G | 20 | *FITM2-R3HDML-HNF4A* | 3758 | 315 | 0.948 | 0.798 | 1.126 | 0.543 | 3758 | 165 | 1.129 | 0.898 | 1.420 | 0.298 |
| rs5945326 | A | X | *DUSP9* | 3589 | 296 | 0.951 | 0.803 | 1.127 | 0.561 | 3589 | 159 | 0.902 | 0.720 | 1.130 | 0.370 |
| rs4812829* | A | 20 | *HNF4A* | 3801 | 317 | 0.99 | 0.82 | 1.18 | 0.88 | 3801 | 170 | 1.050 | 0.830 | 1.330 | 0.700 |
| rs7178572* | G | 15 | *HMG20A* | 3541 | 279 | 0.99 | 0.83 | 1.18 | 0.93 | 3541 | 153 | 1.210 | 0.960 | 1.520 | 0.100 |

| | | | | FBS5,1 AND PPBS =8,5 | | | | | | FBS7,0 AND PPBS =7,8 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | effect allele | Chr | Locus | n | n_cases | OR | CI(lower) | CI(upper) | pval | n | n_cases | OR | CI(lower) | CI(upper) | pval |
| rs2296172 | G | 1 | *MACF1* | 3847 | 96 | 0.958 | 0.603 | 1.523 | 0.856 | 3847 | 27 | 0.772 | 0.304 | 1.959 | 0.585 |
| rs340874 | C | 1 | *PROX1* | 3709 | 92 | 0.897 | 0.672 | 1.197 | 0.460 | 3709 | 25 | 0.917 | 0.532 | 1.583 | 0.757 |
| rs7578597 | T | 2 | *THADA* | 3710 | 93 | 0.727 | 0.498 | 1.061 | 0.099 | 3710 | 25 | 0.744 | 0.360 | 1.538 | 0.425 |
| rs243088 | T | 2 | *BCL 11A* | 3717 | 94 | 0.996 | 0.744 | 1.334 | 0.980 | 3717 | 26 | 0.931 | 0.535 | 1.620 | 0.801 |
| rs998451* | A | 2 | *TMEM163* | 3882 | 98 | 0.749 | 0.487 | 1.153 | 0.190 | 3882 | 26 | 0.735 | 0.318 | 1.700 | 0.472 |
| rs7593730 | T | 2 | *RBMS1/ITGB6* | 3906 | 97 | 0.999 | 0.706 | 1.413 | 0.997 | 3906 | 27 | 1.128 | 0.597 | 2.131 | 0.710 |
| rs7607980 | C | 2 | *COBL1* | 3885 | 97 | 1.325 | 0.869 | 2.019 | 0.191 | 3885 | 27 | 0.809 | 0.317 | 2.070 | 0.659 |
| rs13389219 | C | 2 | *GRB14* | 3829 | 93 | 1.011 | 0.728 | 1.402 | 0.950 | 3829 | 24 | 0.834 | 0.449 | 1.549 | 0.566 |
| rs560887 | C | 2 | *G6PC2/ABCB11* | 3910 | 97 | 0.871 | 0.581 | 1.306 | 0.503 | 3910 | 27 | 1.757 | 0.645 | 4.785 | 0.271 |
| rs7578326 | A | 2 | *KIAA1486/IRS1* | 3600 | 89 | 0.809 | 0.579 | 1.130 | 0.213 | 3600 | 24 | 0.600 | 0.329 | 1.092 | 0.095 |
| rs2943641 | C | 2 | *IRS1* | 3643 | 90 | 0.813 | 0.588 | 1.125 | 0.211 | 3643 | 24 | 0.622 | 0.345 | 1.122 | 0.115 |
| rs4675095 | A | 2 | *IRS1* | 3817 | 93 | 1.092 | 0.703 | 1.699 | 0.695 | 3817 | 25 | 0.808 | 0.380 | 1.721 | 0.581 |
| rs1801282 | C | 3 | *PPARG* | 3652 | 93 | 1.028 | 0.665 | 1.588 | 0.901 | 3652 | 26 | 0.843 | 0.395 | 1.801 | 0.660 |
| rs831571 | C | 3 | *PSMD6* | 3726 | 94 | 1.393 | 0.942 | 2.061 | 0.097 | 3726 | 26 | 1.317 | 0.638 | 2.718 | 0.457 |
| rs4607103 | C | 3 | *ADAMTS9-AS2* | 3884 | 96 | 1.226 | 0.922 | 1.630 | 0.160 | 3884 | 27 | 0.984 | 0.579 | 1.674 | 0.954 |
| rs11708067 | A | 3 | *ADCY5* | 3877 | 95 | 0.995 | 0.706 | 1.402 | 0.978 | 3877 | 26 | 0.661 | 0.367 | 1.193 | 0.169 |
| rs11920090 | T | 3 | *SLC2A2* | 3606 | 91 | 1.607 | 1.001 | 2.580 | 0.050 | 3606 | 24 | 3.025 | 0.931 | 9.827 | 0.066 |
| rs4402960 | T | 3 | *IGF2BP2* | 3750 | 93 | 0.926 | 0.693 | 1.239 | 0.605 | 3750 | 27 | 0.773 | 0.447 | 1.338 | 0.358 |
| rs6815464 | C | 4 | *MAEA* | 3722 | 94 | 1.098 | 0.727 | 1.657 | 0.657 | 3722 | 26 | 1.753 | 0.700 | 4.394 | 0.231 |
| rs10010131 | G | 4 | *WFS1* | 3843 | 93 | 1.270 | 0.910 | 1.772 | 0.160 | 3843 | 25 | 1.365 | 0.714 | 2.613 | 0.347 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs459193 | G | 5 | *ANKRD55* | 3884 | 95 | 0.935 | 0.695 | 1.257 | 0.654 | 3884 | 26 | 0.589 | 0.341 | 1.019 | 0.058 |
| rs4457053 | G | 5 | *ZBED3* | 3579 | 91 | 1.143 | 0.808 | 1.617 | 0.449 | 3579 | 24 | 1.235 | 0.643 | 2.373 | 0.527 |
| rs7754840 | C | 6 | *CDKAL 1* | 3721 | 92 | 0.824 | 0.586 | 1.157 | 0.263 | 3721 | 26 | 0.626 | 0.315 | 1.243 | 0.181 |
| rs7756992 | G | 6 | *CDKAL 1* | 3686 | 92 | 0.776 | 0.548 | 1.098 | 0.152 | 3686 | 26 | 0.817 | 0.431 | 1.550 | 0.537 |
| rs9470794 | C | 6 | *ZFAND3* | 3608 | 92 | 0.856 | 0.538 | 1.362 | 0.511 | 3608 | 24 | 0.995 | 0.428 | 2.318 | 0.991 |
| rs17168486 | T | 7 | *DGKB* | 3855 | 94 | 0.775 | 0.558 | 1.078 | 0.130 | 3855 | 27 | 0.476 | 0.235 | 0.964 | 0.039 |
| rs2191349 | T | 7 | *DGKB/TMEM195* | 3903 | 97 | 1.118 | 0.832 | 1.502 | 0.460 | 3903 | 27 | 2.181 | 1.149 | 4.140 | 0.017 |
| rs864745 | T | 7 | *JAZF1* | 3876 | 96 | 0.946 | 0.693 | 1.290 | 0.724 | 3876 | 27 | 0.667 | 0.387 | 1.147 | 0.143 |
| rs4607517 | A | 7 | *GCK* | 3903 | 96 | 1.000 | 0.652 | 1.535 | 0.998 | 3903 | 27 | 1.338 | 0.648 | 2.762 | 0.431 |
| rs17133918 | T | 7 | *GRB10* | 3907 | 97 | 1.266 | 0.938 | 1.709 | 0.124 | 3907 | 27 | 1.204 | 0.684 | 2.121 | 0.519 |
| rs933360 | A | 7 | *GRB10* | 3905 | 98 | 1.077 | 0.796 | 1.458 | 0.630 | 3905 | 27 | 1.067 | 0.602 | 1.890 | 0.825 |
| rs6943153 | T | 7 | *GRB10* | 3602 | 92 | 0.770 | 0.558 | 1.063 | 0.112 | 3602 | 24 | 1.035 | 0.571 | 1.874 | 0.911 |
| rs1799999* | A | 7 | *PP1R3A* | 3890 | 99 | 0.711 | 0.522 | 0.966 | 0.029 | 3890 | 27 | 0.678 | 0.376 | 1.223 | 0.197 |
| rs6467136 | G | 7 | *GCC1-PAX4* | 3593 | 91 | 1.202 | 0.901 | 1.604 | 0.212 | 3593 | 25 | 2.698 | 1.350 | 5.392 | 0.005 |
| rs516946 | C | 8 | *ANK1* | 3922 | 97 | 1.130 | 0.780 | 1.638 | 0.518 | 3922 | 27 | 1.276 | 0.617 | 2.640 | 0.511 |
| rs896854 | T | 8 | *TP53INP1* | 3903 | 95 | 0.910 | 0.679 | 1.220 | 0.528 | 3903 | 26 | 1.048 | 0.608 | 1.807 | 0.866 |
| rs13266634 | C | 8 | *SLC30A8* | 3898 | 96 | 1.014 | 0.725 | 1.417 | 0.937 | 3898 | 27 | 0.759 | 0.425 | 1.358 | 0.353 |
| rs7034200 | A | 9 | *GLIS3* | 3868 | 96 | 0.797 | 0.599 | 1.060 | 0.118 | 3868 | 27 | 1.153 | 0.676 | 1.965 | 0.601 |
| rs10811661 | T | 9 | *CDKN2A/2B* | 3890 | 95 | 1.082 | 0.699 | 1.673 | 0.724 | 3890 | 27 | 1.184 | 0.510 | 2.751 | 0.694 |
| rs13292136 | C | 9 | *TLE4 (CHCHD9)* | 3706 | 93 | 1.074 | 0.710 | 1.624 | 0.734 | 3706 | 26 | 0.829 | 0.407 | 1.687 | 0.605 |
| rs2796441 | G | 9 | *TLE 1* | 3905 | 97 | 0.983 | 0.737 | 1.311 | 0.908 | 3905 | 27 | 1.024 | 0.595 | 1.760 | 0.933 |
| rs12571751 | A | 10 | *ZMIZ1* | 3601 | 92 | 0.901 | 0.670 | 1.212 | 0.490 | 3601 | 24 | 0.986 | 0.552 | 1.759 | 0.962 |
| rs1111875 | C | 10 | *HHEX* | 3901 | 97 | 0.993 | 0.744 | 1.325 | 0.962 | 3901 | 27 | 0.947 | 0.549 | 1.632 | 0.843 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs553668 | A | 10 | *ADRA2A* | 3666 | 90 | 1.117 | 0.818 | 1.525 | 0.488 | 3666 | 24 | 0.808 | 0.427 | 1.529 | 0.512 |
| rs10885122 | G | 10 | *ADRA2A* | 3683 | 91 | 0.940 | 0.658 | 1.342 | 0.732 | 3683 | 26 | 1.111 | 0.555 | 2.227 | 0.766 |
| rs7903146 | T | 10 | *TCF7L2* | 3543 | 89 | 1.369 | 1.008 | 1.859 | 0.045 | 3543 | 24 | 1.243 | 0.690 | 2.239 | 0.470 |
| rs689* | A | 11 | *INS,INS-IGF2* | 3903 | 97 | 1.227 | 0.860 | 1.752 | 0.260 | 3903 | 27 | 1.886 | 1.037 | 3.432 | 0.038 |
| rs163184 | G | 11 | *KCNQ1* | 3713 | 95 | 0.823 | 0.614 | 1.104 | 0.193 | 3713 | 27 | 1.072 | 0.618 | 1.858 | 0.805 |
| rs2237895 | C | 11 | *KCNQ1* | 3682 | 92 | 0.819 | 0.607 | 1.105 | 0.192 | 3682 | 25 | 1.283 | 0.741 | 2.222 | 0.374 |
| rs5219 | T | 11 | *KCNJ11* | 3595 | 89 | 1.111 | 0.827 | 1.492 | 0.486 | 3595 | 25 | 0.962 | 0.550 | 1.684 | 0.892 |
| rs11605924 | A | 11 | *CRY2* | 3909 | 95 | 0.864 | 0.650 | 1.147 | 0.312 | 3909 | 26 | 1.223 | 0.715 | 2.092 | 0.463 |
| rs7944584 | A | 11 | *MADD* | 3553 | 91 | 0.960 | 0.667 | 1.381 | 0.824 | 3553 | 24 | 0.930 | 0.462 | 1.870 | 0.838 |
| rs174550 | T | 11 | *FADS1* | 3908 | 97 | 1.023 | 0.698 | 1.500 | 0.907 | 3908 | 27 | 1.182 | 0.557 | 2.507 | 0.663 |
| rs1552224 | A | 11 | *CENTD2* | 3911 | 98 | 1.412 | 0.924 | 2.157 | 0.111 | 3911 | 27 | 1.183 | 0.557 | 2.513 | 0.661 |
| rs10830963 | G | 11 | *MTNR1B* | 3714 | 93 | 1.064 | 0.791 | 1.432 | 0.681 | 3714 | 26 | 0.959 | 0.547 | 1.682 | 0.885 |
| rs11063069 | G | 12 | *CCND2* | 3671 | 93 | 0.610 | 0.376 | 0.992 | 0.046 | 3671 | 26 | 0.350 | 0.109 | 1.121 | 0.077 |
| rs10842994 | C | 12 | *KLHDC5* | 3906 | 96 | 0.858 | 0.575 | 1.280 | 0.453 | 3906 | 26 | 0.705 | 0.346 | 1.437 | 0.336 |
| rs1153188 | A | 12 | *DCD* | 3912 | 98 | 1.052 | 0.725 | 1.529 | 0.788 | 3912 | 27 | 1.798 | 0.768 | 4.212 | 0.177 |
| rs1531343 | C | 12 | *HMGA2* | 3915 | 96 | 0.882 | 0.601 | 1.294 | 0.520 | 3915 | 26 | 0.697 | 0.315 | 1.545 | 0.374 |
| rs7961581 | C | 12 | *TSPAN8,LGR5* | 3703 | 93 | 0.800 | 0.581 | 1.101 | 0.171 | 3703 | 26 | 0.869 | 0.482 | 1.567 | 0.640 |
| rs35767 | G | 12 | *IGF1* | 3910 | 98 | 1.301 | 0.900 | 1.880 | 0.162 | 3910 | 27 | 1.012 | 0.526 | 1.946 | 0.971 |
| rs7957197 | T | 12 | *OASL/TCF1/HNF1A* | 3924 | 97 | 1.027 | 0.571 | 1.848 | 0.930 | 3924 | 27 | 0.579 | 0.248 | 1.355 | 0.208 |
| rs9552911* | A | 13 | *SGCG* | 3890 | 97 | 1.031 | 0.653 | 1.626 | 0.896 | 3890 | 27 | 1.257 | 0.567 | 2.787 | 0.574 |
| rs17271305 | G | 15 | *VPS13C* | 3825 | 93 | 0.795 | 0.568 | 1.111 | 0.179 | 3825 | 26 | 0.919 | 0.501 | 1.685 | 0.784 |
| rs11071657 | A | 15 | *FAM148B* | 3897 | 96 | 1.105 | 0.805 | 1.516 | 0.537 | 3897 | 27 | 0.867 | 0.494 | 1.520 | 0.618 |
| rs7177055 | A | 15 | *HMG20A* | 3907 | 96 | 1.044 | 0.783 | 1.391 | 0.770 | 3907 | 27 | 1.219 | 0.709 | 2.096 | 0.475 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11634397 | G | 15 | *ZFAND6* | 3910 | 94 | 0.937 | 0.699 | 1.258 | 0.667 | 3910 | 27 | 0.824 | 0.480 | 1.413 | 0.482 |
| rs8042680 | A | 15 | *PRC1* | 3887 | 95 | 0.772 | 0.577 | 1.034 | 0.083 | 3887 | 27 | 0.832 | 0.480 | 1.441 | 0.511 |
| rs9939609 | A | 16 | *FTO* | 3120 | 68 | 0.836 | 0.575 | 1.216 | 0.349 | 3120 | 21 | 1.120 | 0.596 | 2.103 | 0.726 |
| rs7202877 | T | 16 | *BCAR1* | 3915 | 98 | 0.939 | 0.558 | 1.581 | 0.814 | 3915 | 27 | 1.323 | 0.422 | 4.148 | 0.631 |
| rs8090011 | G | 18 | *LAMA1* | 3911 | 97 | 0.947 | 0.712 | 1.261 | 0.711 | 3911 | 27 | 0.949 | 0.556 | 1.620 | 0.848 |
| rs10401969 | C | 19 | *SUGP1* | 3605 | 91 | 0.916 | 0.552 | 1.520 | 0.735 | 3605 | 24 | 0.807 | 0.289 | 2.253 | 0.682 |
| rs8108269 | G | 19 | *GIPR* | 3508 | 90 | 0.919 | 0.667 | 1.265 | 0.603 | 3508 | 25 | 0.989 | 0.546 | 1.790 | 0.971 |
| rs10423928 | A | 19 | *GIPR* | 3911 | 95 | 0.806 | 0.521 | 1.248 | 0.335 | 3911 | 26 | 0.755 | 0.324 | 1.759 | 0.515 |
| rs6017317 | G | 20 | *FITM2-R3HDML-HNF4A* | 3758 | 94 | 1.089 | 0.806 | 1.470 | 0.578 | 3758 | 27 | 0.751 | 0.419 | 1.345 | 0.335 |
| rs5945326 | A | X | *DUSP9* | 3589 | 89 | 0.834 | 0.620 | 1.124 | 0.233 | 3589 | 23 | 1.078 | 0.594 | 1.956 | 0.804 |
| rs4812829* | A | 20 | *HNF4A* | 3801 | 97 | 0.97 | 0.7 | 1.32 | 0.83 | 3801 | 27 | 0.8 | 0.43 | 1.49 | 0.49 |
| rs7178572* | G | 15 | *HMG20A* | 3541 | 81 | 1.15 | 0.84 | 1.58 | 0.37 | 3541 | 22 | 1 | 0.56 | 1.83 | 0.98 |

# Paper I

# Prevalence and risk factors of gestational diabetes in Punjab, North India: results from a population screening program

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## Abstract

*Objective*: The World Health Organization (WHO) has in 2013 changed the diagnostic criteria for gestational diabetes mellitus (GDM) to acknowledge the putative effect of mildly elevated fasting plasma glucose (FPG) levels on pregnancy outcomes. We aimed to determine the prevalence and risk factors of GDM comparing the previous WHO 1999 criteria to the WHO 2013 criteria in North India.

*Methods*: In a population-based screening programme, 5100 randomly selected North Indian women were studied using a cross-sectional design with a questionnaire, venous FPG and 2-h capillary plasma glucose (PG) after a 75 g oral glucose tolerance test performed between 24 and 28 weeks of pregnancy.

*Results*: The prevalence of GDM was 35% using WHO 2013 criteria vs 9% using WHO 1999 criteria. FPG measurements identified 94% of WHO 2013 GDM cases as opposed to 11% of WHO 1999 GDM cases. In contrast, 2-h PG measurements identified only 13% of WHO 2013 GDM cases compared with 96% of the WHO 1999 GDM cases. Using logistic regression with backward elimination, urban habitat, illiteracy, non-vegetarianism, increased BMI, Hindu religion and low adult height were all independent risk factors of GDM using the 1999 criteria, whereas only urban habitat, low adult height and increased age were independent risk factors of GDM using the 2013 criteria.

*Conclusions*: Intervention studies are needed to justify the WHO 2013 GDM criteria increasing the prevalence four fold to include more than one third of North Indian pregnant women.

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## Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy (1) and was first recognised in 1823 (2). However, there is still no uniform definition of the diagnostic criteria of GDM. GDM is associated with an increased risk of developing type 2 diabetes (T2D) in both mother and child (3), and therefore represents a window of opportunity to prevent diabetes in two generations. However, the antepartum plasma glucose levels that predict macrosomia differ from those that predict later development of prediabetes or diabetes in mothers and their offspring (4), and the extent to which pregnancy complications associated with GDM are determined by increased plasma glucose levels *per se* (fasting or postprandial), or whether they are due to confounding from other common GDM risk factors, is unknown (5).

The World Health Organization (WHO) 1999 criteria defined GDM by fasting plasma glucose (FPG) level $\geq$7.0 mmol/l (126 mg/dl) or 2-h plasma glucose (PG) levels after a 75 g oral glucose tolerance test (OGTT) $\geq$7.8 mmol/l (140 mg/dl). The Indian criteria for GDM use only the 2-h criteria (DIPSI) (6, 7). The prevalence of GDM,

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when using the WHO 1999 criteria range between 1 and 14% in different populations (8, 9, 10).

In order to define the thresholds for FPG and 2-h PG levels after a 75 g OGTT for GDM diagnosis, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study followed 23 000 pregnant women until delivery. This study documented a linear relationship between the level of maternal hyperglycaemia during pregnancy and the risk of complications in both mother and child (11). Importantly, no safe thresholds for FPG or 2-h PG levels were identified below which no association between plasma glucose and pregnancy complications existed. Based on this finding, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) has proposed to lower FPG for diagnosis of GDM, namely to ≥5.1 mmol/l (92 mg/dl) while using a 2-h PG threshold of ≥8.5 mmol/l (153 mg/dl) (12). The World Health Organization (WHO) recently decided to adopt the IADPSG criteria, hereafter named the WHO 2013 criteria (13).

The prevalence of GDM in the HAPO study using the WHO 2013 criteria was ∼18% (14). However, the HAPO study was not population-based, and blinding of investigators and participants for plasma glucose measurements below a predefined level that needed treatment may have precluded some high-risk women from participating in the study (11).

While studies using WHO 1999 criteria have shown that glucose-lowering treatment reduces the risk of pregnancy complications (15, 16), studies to document the cost-effectiveness of screening and introducing glucose-lowering treatment in women with GDM using the proposed WHO 2013 diagnostic criteria are lacking. Consequently, the National Institute of Health, USA, recommended that more knowledge are required to determine the public health consequences of the WHO 2013 criteria before these are universally applied (10). In a recent Norwegian study, the GDM prevalence was 2.4 times higher using the WHO 2013 compared with the WHO 1999 criteria, and the highest risk of GDM of around 40% was found among pregnant women of South Asian ethnic origin (17).

The present study was undertaken to determine the prevalence and risk factors of GDM using the WHO 1999 vs the WHO 2013 criteria in a population-based screening study in the state of Punjab in North India. Furthermore, we aimed to study the extent to which a range of putative GDM risks factors influence risk of GDM by the two different criteria as well as the absolute level of fasting vs 2-h PG levels in the total population of pregnant women.

## Subjects and methods

### Recruitment

To screen a representative group of at least 5000 pregnant women in Punjab, North India, for GDM, all pregnant women in gestational week (GW) 24–28 visiting selected study sites, including departments of obstetrics/gynaecology and diabetes clinics, for antenatal care were approached consecutively during the study period. Nearly all pregnant women in the region attend antenatal care, and only a few women from the upper middle class or with a high socio-economic status attend private hospitals.

A multistage random screening technique was applied to ensure representative participation of women. Multistage refers to the process of first choosing three representative regions in Punjab, then sub-staging into three different hospitals that provided most of the population with health care, and finally recruiting pregnant women visiting antenatal clinics. Thus, this cross-sectional study not only screened women who were considered at high risk of developing GDM, but called for universal screening of all pregnant women irrespective of age, BMI, family history of diabetes, religion, diet, socio-economic status or residence. Women with pre-gestational diabetes were excluded from the study.

The data were collected from August 2009 until December 2012. During this period there were ∼12 000 births at the selected study sites. In total, 6255 women were invited to participate, of which 1014 declined participation (Fig. 1). Consequently, 5241 women were screened for GDM. Due to missing data related to glucose measurements, age and/or BMI, data from 141 women were not included in the statistical analyses, resulting in 5100 participants, i.e., a participation rate of 81.5%. The main reason for declining participation was fear of GDM diagnosis as it is considered a social stigma. Lack of time due to household routines (mainly urban) and demands put on daily wagers and labourers (mainly rural) were additional reasons for not participating.

All information material and consent forms were in three languages, including Hindi (National), Punjabi (Regional), and English. Informed written consent was obtained according to the Indian Medical Research Council (ICMR, New Delhi) guidelines in the form of a signature or a thumb impression (a proxy for illiterate subjects). The study was approved by the Regional Ethics Committee and by the Directorate of Medical Research Education of India.

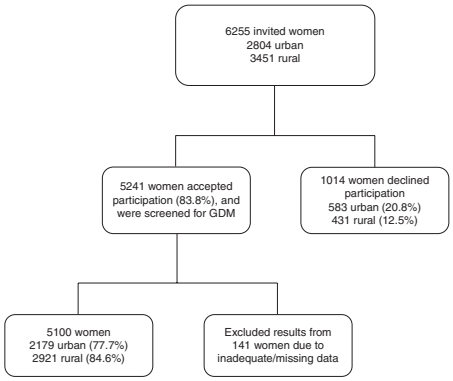


**Figure 1**
Participant inclusion.

### Setting

To represent the main health care systems in Punjab, nine prominent hospitals were chosen as study sites; namely three public hospitals from different districts run by the government, three primary health centres – governmental subunits located in rural areas – and three private hospitals. At each hospital, a team of paramedical staff, nurses/mid-wives or diabetic educators were assigned to inform and recruit eligible pregnant women as well as to perform the GDM screening.

### Variables collected

All women were subjected to personal interviews using a structured questionnaire, which was subsequently filled out by the personnel. The questions asked included age, place of residence (rural/urban), education status (educated if able to provide a signature, and illiterate if only able to give a thumb impression), religion, diet (vegetarianism), family history of diabetes (irrespective of type, in first- and second-degree relatives), parity, present and past obstetric history with any complication, history of any specific medications as well as age at marriage. The GW was calculated from the first day of the woman's last menstrual period as recorded on the antenatal card. Furthermore, weight and height was measured and recorded by standard methods for each subject and the BMI (kg/m$^2$) calculated.

The majority (~70%) of the pregnant women came in the fasting state defined as an overnight fast of 8–12 h. Women who were not fasting were asked to come back the next day, and only fasting women were thus included in the study. The women who were not fasting the first day and who despite the invitation did not show up the following day were counted as having declined participation (Fig. 1). To ensure uniformity of all procedures, guidelines and protocols were distributed to all medical and paramedical personnel involved in the study and training sessions were held on a regular basis.

A fasting venous blood sample was drawn from an antecubital vein in 10 ml EDTA vacutainers (no fluoride). Venous samples were drawn only in the fasting state to avoid discomfort from sitting with the syringe during the 2-h OGTT. For the 2-h plasma glucose measurements during the OGTTs as described below, we used capillary blood samples. The approach of using 2-h capillary glucose measurements is in accordance with routine practice in many low-income settings including Punjab. Before centrifugation of venous samples, FPG concentration was measured using Accu-Chek glucometers (Roche Diagnostics). Glucometers were calibrated as recommended and measurements were further validated in a subset of women as described below. The glucometer was used for both fasting and post-glucose load measures at a main assembly site of laboratory and bed-side sampling.

OGTT procedures were standardized and performed the same way at all sites. Briefly, the women were requested to drink the 250 ml glucose solution within 5 min, and 2 h after finalizing the glucose ingestion, a single-prick capillary plasma glucose (CPG) concentration was measured using the Accu-Chek glucometer.

### Comparative analyses of capillary vs venous plasma glucose

In a randomly chosen subset of 183 women, two samples were drawn simultaneously 2 h after the OGTT for comparative analyses of CPG measured at bed-side by glucometers with venous plasma glucose levels (VPG) measured in the laboratory by the glucose oxidase peroxidase (GOD-POD) method (Microlab 300, Merck Diagnostics) (18). The mean difference in plasma glucose measurements between the two methods was 15%, with the CPG values being higher, which is in accordance with previous reports (19). Accordingly, the post-OGTT CPG measurements were corrected (reduced) by 15%, and with the WHO criteria of GDM, the 2-h cut-off level of 7.8 mmol/l being equal to a measured CPG level of 8.9 mmol/l. There was a significant positive correlation between the CPG and VPG levels ($r=0.82$, $P<0.0001$).

### Statistics

Due to the proposal by WHO to lower the fasting diagnostic criteria for GDM, as well as the *a priori* assumption that this might significantly change the prevalence and the characteristics of GDM women in a native Asian setting, separate analyses of prevalence and risk factors was performed based on relevant selected fasting cut-off levels only. ANOVA was used to compare group means of FPG and 2-h PG levels as well as group means of non-GDM and GDM women. The $\chi^2$ test (Pearson) was used for comparison of group frequencies. Multivariate logistic regression analysis with backward elimination of independent variables was used to test the relationship between GDM and variables possibly related to GDM. A linear regression analysis with backward elimination of independent variables was used to test the relationship between FPG and 2-h PG and variables possibly influencing FPG and 2-h PG. All statistical analyses were performed using Stata 13 (StataCorp, College Station, TX, USA). Two-sided $P$ values of $<0.05$ were considered statistically significant.

## Results

### Subject characteristics

A total of 5100 pregnant women were included in the study. When applying both diagnostic criteria, GDM women had significantly higher FPG and 2-h PG levels ($P<0.001$) compared to non-GDM women. GDM women had increased BMI ($P=0.01$), were older ($P<0.001$) and shorter ($P=0.01$) applying WHO 2013, and were shorter ($P<0.001$) using WHO 1999 criteria compared to non-GDM women (Table 1). Furthermore, non-GDM women had significantly higher FPG ($P<0.0001$) and 2-h PG ($P=0.004$) when applying WHO 1999 criteria, whereas the GDM women had significantly higher 2-h PG ($P<0.0001$) and significantly lower age ($P=0.02$) and height ($P=0.01$) when diagnosed using WHO 1999 as compared to WHO 2013 criteria.

The risk factor distribution is shown in Table 2. The women had a mean age of 21.5±3.3 years, BMI of 24.2±4.4 kg/m$^2$ and a mean GW of 25.4±2.5 weeks (mean±S.D.). Information regarding parity was only obtained for 42% of the women, and of these 78% were primipara. As shown in Table 2, the mean FPG ($P<0.001$) and 2-h PG ($P<0.001$) levels were significantly higher in urban compared to rural women. Furthermore, in the unadjusted analyses, Sikh women displayed higher mean FPG ($P=0.04$) and 2-h PG ($P<0.001$) levels compared to Hindu women. Interestingly, vegetarian women displayed significantly increased mean FPG levels compared to non-vegetarian women ($P=0.004$) with no differences between groups for the 2-h PG levels ($P=0.45$). Both FPG and 2-h PG increase with age ($P<0.001$ for both) as well as with BMI ($P<0.001$ for both). Women with a family history of diabetes had increased FPG levels and 2-h PG ($P<0.001$ for both). Finally, there was no statistically significant difference in FPG between illiterate vs illiterate women ($P=0.06$), whereas the 2-h PG level was significantly increased ($P=0.05$) among illiterate compared to literate women (Table 2).

### Prevalence of GDM

The overall prevalence of GDM was 9.0% using the WHO 1999 diagnostic criteria (Table 3). However, it increased to 34.9% when applying WHO 2013 criteria. The FPG measurements identified 94% of WHO 2013 GDM cases as opposed to 11% of WHO 1999 GDM cases (Supplementary Table 2, see section on supplementary data given at the end of this article). In contrast, 2-h PG

**Table 1** Baseline characteristics for non-GDM and GDM women for FPG, 2-h PG, BMI, age and height when applying the WHO 2013 and WHO 1999 criteria respectively. Data are mean±S.D. Comparisons of mean values are performed by ANOVA.

| | WHO 2013 | | | WHO 1999 | | | WHO 2013 vs 1999 | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Non-GDM | GDM |
| **Variables** | Non-GDM ($n=3321$) | GDM ($n=1779$) | ***P* value** | Non-GDM ($n=4642$) | GDM ($n=458$) | ***P* value** | *P* value | *P* value |
| FPG (mmol/l) | 4.44±0.49 | 5.51±0.68 | <0.001 | 4.75±0.65 | 5.47±1.28 | <0.001 | <0.0001 | 0.44 |
| 2-h PG (mmol/l) | 5.88±1.02 | 6.87±1.66 | <0.001 | 5.95±0.93 | 9.07±1.74 | <0.001 | 0.004 | <0.0001 |
| BMI (kg/m$^2$) | 24.1±4.28 | 24.4±4.48 | 0.01 | 24.2±4.3 | 24.5±4.8 | 0.15 | 0.33 | 0.83 |
| Age (years) | 21.4±3.3 | 21.7±3.4 | <0.001 | 21.5±3.3 | 21.3±3.5 | 0.16 | 0.07 | 0.02 |
| Height (cm) | 148±15 | 147±14 | 0.01 | 148±15 | 145±14 | <0.001 | 0.70 | 0.01 |

**Table 2** Mean FPG and 2-h PG levels in relation to subject characteristics (unadjusted data). Data are mean ± S.D. Applying a *post-hoc* test with Sidak correction, significant differences were found between the following categories: $P \leq 0.05$, FPG: (Hindu and Sikh), (age ≤20 and age >30), (BMI <20 and 25≤BMI<30), (20≤BMI<25 and 25≤BMI<30). 2-h PG: (age ≤20 and age >30); $P \leq 0.001$, FPG: (age ≤20 and 20<age≤25), (age ≤20 and 25<age≤30), (25<age≤30 and age >30), (BMI <20 and BMI ≥30), (20≤BMI<25 and BMI ≥30). 2-h PG: (Hindu and Sikh), (age ≤20 and 20<age≤25), (age ≤20 and 25<age≤30), between all BMI categories.

| | *n* (%) | FPG (mmol/l), Mean ± S.D. | *P* ANOVA | 2-h PG (mmol/l), Mean ± S.D. | *P* ANOVA |
|---|---|---|---|---|---|
| Total | 5100 (100) | 4.81 ± 0.76 | | 6.23 ± 1.36 | |
| Habitat | | | | | |
| Rural | 2921 (57.27) | 4.77 ± 0.71 | <0.001 | 6.16 ± 1.30 | <0.001 |
| Urban | 2179 (42.73) | 4.86 ± 0.82 | | 6.31 ± 1.44 | |
| Religion | | | | | |
| Hindu | 2788 (54.67) | 4.79 ± 0.76 | 0.04 | 6.16 ± 1.44 | <0.001 |
| Sikh | 2210 (43.33) | 4.84 ± 0.77 | | 6.31 ± 1.24 | |
| Others | 102 (2.00) | 4.75 ± 0.77 | | 6.33 ± 1.53 | |
| Diet | | | | | |
| Vegetarian | 3048 (59.76) | 4.84 ± 0.79 | 0.004 | 6.24 ± 1.29 | 0.45 |
| Non-vegetarian | 2052 (40.24) | 4.77 ± 0.71 | | 6.21 ± 1.47 | |
| Age (years) | | | | | |
| Age ≤20 | 2068 (40.55) | 4.74 ± 0.79 | <0.001 | 6.02 ± 1.42 | <0.001 |
| 20<age≤25 | 2448 (48.00) | 4.85 ± 0.72 | | 6.34 ± 1.33 | |
| 25<age≤30 | 540 (10.59) | 4.94 ± 0.78 | | 6.47 ± 1.19 | |
| Age >30 | 44 (0.86) | 4.89 ± 0.96 | | 6.56 ± 1.15 | |
| BMI (kg/m$^2$) | | | | | |
| BMI <20 | 885 (17.35) | 4.75 ± 0.71 | <0.001 | 5.86 ± 1.38 | <0.001 |
| 20≤BMI<25 | 2221 (43.55) | 4.78 ± 0.74 | | 6.11 ± 1.43 | |
| 25≤BMI<30 | 1523 (29.86) | 4.86 ± 0.81 | | 6.48 ± 1.20 | |
| BMI ≥30 | 471 (9.24) | 4.93 ± 0.77 | | 6.65 ± 1.26 | |
| Family history | | | | | |
| Yes | 1938 (38.00) | 4.89 ± 0.69 | <0.001 | 6.60 ± 1.15 | <0.001 |
| No | 3162 (62.00) | 4.76 ± 0.79 | | 6.00 ± 1.43 | |
| Literacy | | | | | |
| Illiterate | 1679 (32.92) | 4.84 ± 0.79 | 0.06 | 6.28 ± 1.49 | 0.05 |
| Literate | 3421 (67.08) | 4.80 ± 0.74 | | 6.20 ± 1.30 | |

measurements identified only 13% of WHO 2013 GDM cases compared to 96% of the WHO 1999 GDM cases.

Figure 2 shows the relationship between FPG and 2-h PG levels in the women. Although the FPG and 2-h PG values were clearly correlated, the diversity of measurements was increasing with increased values of both measurements, resulting in not only markedly different prevalence of GDM with the WHO 1999 (blue) vs the WHO 2013 (red) criteria. Furthermore, the figure reveals that different women are classified as GDM when using the WHO 1999 vs WHO 2013 criteria.

When looking at the prevalence according to risk factor, urban women had a significantly increased GDM prevalence compared to rural women using both GDM criteria ($P<0.001$ for WHO 2013 and $P=0.001$ for WHO 1999) (Table 3). The GDM prevalence was increased in Hindu as compared to Sikh women using WHO 1999 criteria only (overall $P=0.02$). Interestingly, vegetarianism unadjusted for confounders resulted in a significantly higher GDM prevalence than non-vegetarianism when WHO 2013 criteria was applied ($P=0.04$), while non-vegetarian women had significantly higher prevalence when WHO1999 criteria were applied ($P=0.001$) (Table 3). Age was associated with an increasing GDM prevalence using the WHO 2013 criteria ($P=0.004$), and there was no effect of increasing BMI on GDM prevalence using either criteria. Family history of diabetes was not associated with increased prevalence of GDM. Illiteracy among pregnant women was associated with increased GDM prevalence compared to literate women using the WHO 1999 criteria only ($P<0.001$).

## Regression analyses

A multivariate logistic regression with backward elimination of independent variables was used to test the relationship between GDM and variables possibly related to GDM (Table 4). A linear regression analysis with backward elimination of independent variables was used to test the relationship between FPG and 2-h PG and

**Table 3** Prevalence (%) of GDM according to GDM diagnostic criteria (unadjusted data). Overall *P* value is determined by a Pearson's $\chi^2$ test. Applying a *post-hoc* test with Sidak correction, significant differences were found between the following categories: WHO 2013, age ≤20 and 20<age≤25 ($P=0.003$), age ≤20 and 25<age≤30 ($P=0.005$); WHO 1999, Hindu and Sikh ($P=0.01$).

| | WHO 2013 | | WHO 1999 | |
|---|---|---|---|---|
| | FPG ≥5.1 or 2-h PG ≥8.5 (mmol/l) ($n=1779$) | *P* value | FPG ≥7.0 or 2-h PG ≥7.8 (mmol/l) ($n=458$) | *P* value |
| Overall prevalence (%) | 34.9 | | 9.0 | |
| According to risk factor (%) | | | | |
| Habitat | | | | |
| Rural | 31.9 | <0.001 | 7.9 | 0.001 |
| Urban | 38.8 | | 10.5 | |
| Religion | | | | |
| Hindu | 34.5 | 0.78 | 9.8 | 0.02 |
| Sikh | 35.2 | | 7.8 | |
| Others | 37.3 | | 12.8 | |
| Diet | | | | |
| Vegetarian | 36.0 | 0.04 | 7.9 | 0.001 |
| Non-vegetarian | 33.2 | | 10.6 | |
| Age (years) | | | | |
| Age ≤20 | 32.1 | 0.004 | 8.7 | 0.87 |
| 20<age≤25 | 36.3 | | 9.2 | |
| 25<age≤30 | 38.5 | | 9.1 | |
| Age >30 | 43.2 | | 11.4 | |
| BMI (kg/m$^2$) | | | | |
| BMI <20 | 33.0 | 0.24 | 8.7 | 0.26 |
| 20≤BMI<25 | 34.3 | | 9.1 | |
| 25≤BMI<30 | 35.9 | | 8.3 | |
| BMI ≥30 | 37.8 | | 11.3 | |
| Family history | | | | |
| Yes | 35.2 | 0.67 | 9.0 | 0.99 |
| No | 34.7 | | 9.0 | |
| Literacy | | | | |
| Illiterate | 36.3 | 0.13 | 11.3 | *P*<0.001 |
| Literate | 34.2 | | 7.8 | |

possibly related variables (Table 5). The full model included the following variables: habitat_rural, religion_Sikh, religion_Hindu, diet_non-vegetarian, age, height, BMI, family history and literate. Age, height and BMI were continuous variables. The backward elimination was applied to reduce the variable set to include only significant variables as presented in Tables 4 and 5.

In the reduced model including all 5100 women, analysis using the presence or absence of GDM as dependent variable and subject characteristics as independent variables showed that when applying the WHO 2013 criteria, urban habitat ($P<0.001$), increasing age ($P=0.001$) and decreasing height ($P=0.001$) were significant independent GDM risk factors (Table 4). When using the WHO 1999 diagnostic criteria, independent GDM risk factors were urban habitat ($P=0.001$), Hindu religion ($P<0.001$), illiteracy ($P<0.000$), non-vegetarian diet ($P<0.001$), decreasing height ($P<0.001$) and increasing BMI ($P=0.02$) (Table 4).

Independent variables associated with FPG were urban habitat ($P<0.001$), family history ($P=0.003$), illiteracy ($P=0.007$), age ($P<0.001$) and BMI ($P<0.001$), whereas independent variables associated with 2-h PG were urban habitat ($P<0.001$), height ($P<0.001$), illiteracy ($P<0.001$), BMI ($P<0.001$) and family history ($P<0.001$) (Table 5).

## Discussion

In this study of 5100 North Indian pregnant women, we showed an almost four-fold difference (9.0% vs 34.9%) in the prevalence of GDM in North India when comparing the WHO 1999 to the new WHO 2013 criteria. Several distinct factors, including BMI, education (illiteracy), habitat and family history of diabetes all independently influenced both FPG and 2-h PG concentrations. However, increased FPG was also significantly influenced by increasing age and, somewhat paradoxically, by a

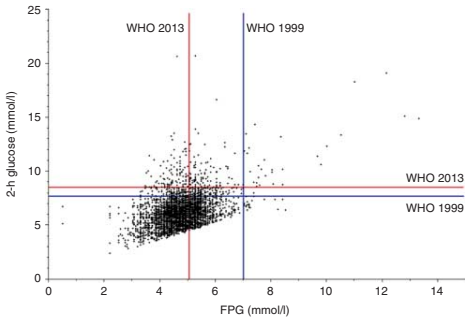


**Figure 2**

Relationship between fasting plasma glucose (FPG) vs 2-h plasma glucose (2-h PG) values during oral glucose tolerance tests for 5100 women. WHO 2013 cut-off is shown in red and WHO 1999 in blue. The figure illustrates that the relationship is not straight forward nor linear, that in particular the different FPG cut-off levels create the large differences in GDM prevalence, and that different women are classified as having GDM using the two criteria. The percentage of women classified as having GDM was 7.2% by both criteria, 1.8% by the 1999 criteria only, and 27.7% by the 2013 criteria only. The remaining 63.3% of all women were classified as non-GDM using both criteria.

vegetarian diet, whereas increased 2-h PG was influenced independently by low adult height. Thus, the relationship between FPG and 2-h PG measurements was not straightforward (Fig. 2), and defining GDM by the somewhat arbitrary WHO 1999/DIPSI vs WHO 2013 criteria identified different distinct risk factors.

Our finding of a higher GDM prevalence of 34.9% using the WHO 2013 criteria, compared to the HAPO study reporting a prevalence of ~18 and ~24% among Asian women (20), may reflect differences in inclusion criteria. Importantly, we included women from the lowest socio-economical classes, many of whom are living in rural areas. Asian women included in the HAPO study were from the most developed Asian cities, Shanghai and Singapore, and may not be entirely representative for the quantitatively largest proportion of women in Asia. From a pilot survey, we were informed by the health authorities maintaining records at the study sites that the average age of women giving birth at the chosen sites was between 20 and 23 years, and that 65–70% were primipara. However, due to a lack of exact records of all of the estimated 12 000 women giving births at the different study sites during the entire period, the extent to which the 5100 women included in the study are fully representative of the population cannot be guaranteed. Overall, the women included in the study were relatively young and predominantly primipara, meaning that we theoretically could have underestimated the true prevalence of GDM.

Our finding of a GDM prevalence of 34.9% using WHO 2013 criteria in North Indian women appears inconsistent with the recently reported prevalence of 14.6% in South Indian women (9). This may be due to a different genetic and cultural admixture of North vs South Indian women. However, this is unlikely to be the full explanation for the more than two-fold difference in GDM prevalence between the studies, and it is noteworthy that the former study, in contrast to our data, reported no significant difference in GDM prevalence using WHO 2013 vs WHO 1999/DIPSI criteria (9). Interestingly, our GDM prevalence using WHO 2013 criteria of 34.9% was close to that of 37% reported among a group of ethnic minority women in Norway (17).

BMI was not an independent risk factor of GDM using the WHO 2013 criteria, and was only weakly associated with increased risk of GDM using the WHO 1999 criteria

**Table 4** Logistic regression analysis with backward elimination of independent variables possibly influencing GDM diagnosis applying the WHO 2013 and WHO 1999 criteria. Data are odds ratios (OR) with 95% CI. The full model included the following: habitat_rural, religion_Sikh, religion_Hindu, diet_non-vegetarian, age, height, BMI, family history and literate. Age, height and BMI were continuous variables.

| **Independent variables applying Criteria** (WHO 2013/WHO1999) | **OR (95% CI)** | ***P* value** |
|---|---|---|
| WHO 2013 | | |
| Habitat (rural vs urban) | 0.74 (0.66–0.83) | <0.001 |
| Age[a] | 1.10 (1.04–1.17) | 0.001 |
| Height[a] | 0.92 (0.87–0.98) | 0.005 |
| Diet (non-vegetarian vs vegetarian) | 0.91 (0.80–1.02) | 0.09 |
| Constant | 0.82 (0.42–1.60) | 0.55 |
| WHO 1999 | | |
| Habitat (rural vs urban) | 0.72 (0.60–0.88) | 0.001 |
| Religion Sikh | 0.69 (0.56–0.85) | <0.001 |
| Literacy (literate vs illiterate) | 0.69 (0.57–0.85) | <0.001 |
| Diet (non-vegetarian vs vegetarian) | 1.44 (1.18–1.75) | <0.001 |
| Height[a] | 0.99 (0.98–0.99) | <0.001 |
| BMI[a] | 1.12 (1.02–1.24) | 0.02 |
| Constant | 0.47 (0.14–1.55) | 0.21 |

[a]OR resulting from an increase of one S.D.

**Table 5** Linear regression analysis with backward elimination of independent variables possibly influencing FPG and 2-h PG. Data are β coefficient with 95% CI. The full model included the following: habitat_rural, religion_sikh, religion_hindu, diet_non-vegetarian, age, height, BMI, family history and literate. Age, height and BMI were continuous variables.

| Independent variables for FPG/2-h PG | *β* coefficient (95% CI) | *P* value |
|---|---|---|
| FPG | | |
| Habitat (rural vs urban) | −0.09 (−0.13 to −0.05) | <0.001 |
| Family history | 0.07 (0.02 to 0.12) | 0.003 |
| Literacy | −0.06 (−0.11 to −0.02) | 0.007 |
| Diet (non-vegetarian vs vegetarian) | −0.04 (−0.08 to 0.0003) | 0.05 |
| Age | 0.01 (0.006–0.02) | <0.001 |
| BMI | 0.01 (0.004–0.02) | <0.001 |
| Constant | 4.39 (4.21–4.56) | <0.001 |
| 2-h PG | | |
| Habitat (rural vs urban) | −0.16 (−0.23 to −0.08) | <0.001 |
| Religion Sikh | −0.07 (−0.14 to 0.01) | 0.10 |
| Height | −0.007 (−0.010 to −0.004) | <0.001 |
| Literacy | −0.17 (−0.25 to −0.09) | <0.001 |
| Age | 0.01 (−0.001 to 0.02) | 0.08 |
| BMI | 0.04 (0.02–0.05) | <0.001 |
| Family history | 0.48 (0.40–0.57) | <0.001 |
| Constant | 6.13 (5.65–6.61) | <0.001 |

(Table 4). Reasons for the weak or missing impact of BMI on GDM risk may be that BMI determinations were based on weight in GW 24–28, as well as the possibility that the effect of BMI to some extent may be mediated via other factors such as non-vegetarian diet. Other recent studies have reported a weak impact of BMI on risk of T2D in a low income country (21).

Increasing age is major risk factor for T2D (22, 23). Increasing age was independently associated with increasing FPG but not significantly with increased 2-h PG levels in the linear regression analysis including all 5100 pregnant North Indian women. Thus, the overall effect of age on plasma glucose levels was weak and, in accordance with the regression analyses, increased age was only identified as an independent risk factor of GDM using the WHO 2013 and not the WHO 1999 criteria (Table 5). The age effect may be explained by the decline in pancreatic insulin secretion capacity with age (24, 25), and indeed decreased insulin secretion may influence FPG levels relatively more than the 2-h PG levels, which in contrast may be relatively more influenced by insulin resistance (26).

Illiteracy is a proxy of social class and was also independently associated with increased FPG and 2-h PG measurements in the entire group of women. However, the relative impact (*β* coefficients, Table 5) of illiteracy was more pronounced on the 2-h PG compared with the FPG measurements, which in turn may explain why illiteracy was only identified as an independent risk factor of GDM using the WHO 1999 compared with WHO 2013 criteria (Table 4). Other studies have previously found indications of a low social class and poverty being associated with increased risk of developing GDM (8, 27). The explanation for this is unknown, but may include a lower degree of physical activity, differences in diet compositions and body composition factors beyond BMI (such as lower muscle mass), a more adverse intrauterine environment, increased exposure to toxic endocrine disruptors and/or other factors such as low vitamin B12 levels (28) associated with poverty in India.

Adult height is another factor associated with social class and may to some extent express growth 'stunting'. Indeed, low adult height was identified as an independent risk factor of GDM, even above and beyond the effect of illiteracy, using both the WHO 1999 as well as the WHO 2013 criteria (Table 4). Besides social class, adult height may be a marker of early pre- and post-natal nutrition and growth, and may to some extent support the role of the early environment and developmental programming on risk of developing GDM in India (29).

Vegetarianism is a lifestyle chosen by around 50% of all Indians. In the linear regression analyses we found that vegetarianism was not statistically significantly associated with FPG or 2-h PG levels (Table 5). However, in the logistic regression analysis, non-vegetarianism was associated with increased risk of developing GDM by the WHO 1999 but not WHO 2013 criteria (Table 4). Other studies have previously reported vegetarianism to be associated with reduced risk of GDM (30), and may be explained by

the beneficial effect of vegetables on glucose regulation (31, 32). The reason for the differential effect of vegetarianism on FPG vs 2-h PG levels, explaining the differential impact of vegetarianism on risk of GDM using WHO 1999 or WHO 2013 criteria, may be a somewhat different and skewed distribution of FPG levels among vegetarian compared with non-vegetarian women. This in turn could be due to their lower BMI (Supplementary Table 1, see section on supplementary data given at the end of this article) or perhaps to an insufficient protein, zinc or vitamin D intake.

In accordance with other studies in low- and middle-income countries, we identified a strong positive impact of urban vs rural habitat on FPG and on 2-h PG levels (Table 5), as well as on the risk of GDM using both the WHO 1999 and 2013 criteria (Table 4). This may be due to a general lower level of physical activity, unhealthier diet, low B12 or B12/folate imbalance, as well as other factors such as increased pollution in urban compared to rural habitats (27, 28, 33, 34).

Family history of diabetes is another conventional risk factor of GDM and is supposed to represent the genetic risk dimension of the disease (33). Indeed, family history of diabetes was independently associated with increased FPG as well as increased 2-h PG levels among all women in the analyses. However, family history of diabetes was not identified as an independent risk factor of GDM using either the WHO 1999 or the WHO 2013 criteria (Table 4). This suggests that the chosen cut-off levels defining GDM by either the WHO 1999 or the WHO 2013 criteria may not appropriately reflect the otherwise documented impact of family history of diabetes on FPG and 2-h PG levels, and consequently that analyses of genetic risk factors of glucose intolerance in pregnancy among Indian women should apply analytical approaches to determine the impact of genetic determinants (SNPs) on plasma glucose levels irrespective of any of the currently proposed or applied diagnostic GDM criteria. Another reason for the absent impact of family history of diabetes on risk of GDM could be that 38% of all pregnant women showed a relatively strong family history of diabetes, thereby decreasing its specificity as a risk factor. Finally, the genetic dimension could be inherent in the religion category and explain the increased risk of GDM among Hindu vs Sikh women using the WHO 1999 criteria (Table 4). Whether this difference may be due to variations in body composition, including muscle mass, and/or genetic differences in insulin secretion and/or insulin action remains to be determined. The somewhat paradoxical finding of increased GDM prevalence among Hindu vs Sikh women using the WHO 1999 criteria, despite slightly higher mean FPG and 2-h PG values among Sikh women, may be explained by differences in distribution and range of plasma glucose levels in the two groups.

We used standard Accu-Chek bedside glucometers to determine the FPG and 2-h PG levels. The 2-h PG measurements were validated in a subset of women using a standardized GOD-POD method, and in accordance with previous results (19) we found an acceptable concordance between the two measurements. This supports the conclusion that bedside glucometers can be used as a cost-effective GDM screening solution in a low-income setting (18, 19, 20). Accordingly, the current study proved to be the most cost-effective among all of the included screening programs in a recent report (22, 21). Furthermore, the overall attendance rate of 82% compared with 54% in the HAPO study (7) and 74% in a recent Norwegian GDM screening study (35) is high, and the results are therefore likely to be representative for the general population of Punjab. For reasons of convenience, we used capillary blood samples for the 2-h PG measurements, which due to the fluctuating plasma glucose levels after glucose ingestion exhibit a higher variability compared with fasting measurements obtained during steady state glucose levels. This may to some unknown extent contribute to the relatively large variation between fasting and 2-h PG measurements across the full range of glucose tolerance status as illustrated in Fig. 2, and may have caused some degree of misclassification of cases with 2-h PG measurements near the respective GDM cut-off levels. However, given that the variability of measurements influence glucose measurements in both directions, this is unlikely to have influenced the GDM prevalence determinations.

The new WHO 2013 criteria in addition recommend 1-h post-OGTT PG measurements, which was not performed in this study, initiated before these criteria were ultimately defined. However, inclusion of 1-h PG measurements could only increase the already extremely high GDM prevalence using the WHO 2013 criteria fasting and 2-h cut-off levels.

The data available for the current study does not include pregnancy outcomes. While follow-up studies of mothers and offspring are planned for the future, it needs to be emphasized that such studies will not answer the most crucial questions of the causality of adverse outcomes associated with GDM. A meta-analysis from 2008 concluded that there is insufficient evidence to show beneficial effects of intensive glucose-lowering treatment for long-term adverse GDM complications, including risk of dysmetabolic traits in the offspring (23). Importantly,

it was mentioned that potential residual confounding risk factors such as educational status, body fat content and distribution, urbanisation, etc., and not necessarily elevated plasma glucose level *per se*, might be responsible for some adverse pregnancy outcomes associated with GDM. This may in particular be the case for the mildest elevations of plasma glucose levels in pregnancy, which was a major argument for the US committee not to endorse the proposed GDM criteria by the IASDPG (10).

The group defined as literate in this study may have included an unknown proportion of women with limited writing skills who are likely also to have been defined as illiterate women if more elaborate tests had been used. Nevertheless, using the very simple criteria of being able to write own name, we identified the one third of all of the screened women with the lowest degree of education, justifying our approach in this unique low-income North Indian setting.

Taken together, we have shown that GDM would affect more than one third of all pregnant women in North India if the WHO 2013 GDM criteria were implemented. However, there is insufficient knowledge of the short- and long-term clinical outcomes of lifestyle as well as pharmacological interventions against GDM using WHO 2013 criteria, and therefore it can be questioned whether these criteria really should be endorsed uncritically in India. Besides being associated with enormously increased health care expenditures, defining every third Indian woman with a GDM diagnosis carries with it an important personal adverse stigmatizing dimension, since being diagnosed with diabetes in India may have strong social consequences for a young woman. Altogether, we therefore recommend awaiting further significant outcome data before introducing the proposed WHO 2013 criteria in India.

**Supplementary data**

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-14-14-0428.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Author contribution statement**

G P Arora designed the study, acquired data, analysed and interpreted data and drafted the manuscript. R G Thaman, R B Prasad and C Brøns interpreted data and drafted the manuscript. P Almgren performed statistical analyses. L C Groop and A A Vaag designed the study, interpreted data and drafted the manuscript. All authors have approved the final version of the manuscript to be published.

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**Supplementary Table 1**. Distribution of women according to risk factors.

| | | | Habitat | | Religion | | |
|---|---|---|---|---|---|---|---|
| Characteristics | N | % | Rural | Urban | Hindu | Sikh | Others |
| **Habitat** | | | | | | | |
| Rural | 2921 | 57.3 | | | 1736 | 1124 | 61 |
| *%* | | | | | *59.4* | *38.5* | *2.1* |
| Urban | 2179 | 42.7 | | | 1052 | 1086 | 41 |
| *%* | | | | | *48.3* | *49.8* | *1.9* |
| **Religion** | | | | | | | |
| Hindu | 2788 | 54.7 | 1736 | 1052 | | | |
| *%* | | | *62.3* | *37.7* | | | |
| Sikh | 2210 | 43.3 | 1124 | 1086 | | | |
| *%* | | | *50.9* | *49.1* | | | |
| Others | 102 | 2.00 | 61 | 41 | | | |
| *%* | | | *59.8* | *40.2* | | | |
| **Dietary Pattern** | | | | | | | |
| Vegetarian | 3048 | 59.8 | 1784 | 1264 | 1808 | 1205 | 35 |
| *%* | | | *58.5* | *41.5* | *59.3* | *39.5* | *1.1* |
| Non-vegetarian | 2052 | 40.2 | 1137 | 915 | 980 | 1005 | 67 |
| *%* | | | *55.4* | *44.6* | *47.8* | *49.0* | *3.3* |
| **Age (years)** | | | | | | | |
| Age ≤ 20 | 2068 | 40.5 | 1217 | 851 | 1413 | 595 | 60 |
| *%* | | | *58.8* | *41.2* | *68.3* | *28.8* | *2.9* |
| 20 < age ≤ 25 | 2448 | 48 | 1367 | 1081 | 1148 | 1264 | 36 |
| *%* | | | *55.8* | *44.2* | *46.9* | *51.6* | *1.5* |
| 25 < age ≤ 30 | 540 | 10.6 | 311 | 229 | 212 | 322 | 6 |
| *%* | | | *57.6* | *42.4* | *39.3* | *59.6* | *1.1* |
| Age > 30 | 44 | 0.9 | 26 | 18 | 15 | 28 | 1 |
| *%* | | | *59.1* | *40.9* | *34.1* | *63.6* | *2.3* |
| **BMI** | | | | | | | |
| BMI < 20 | 885 | 17.3 | 481 | 404 | 629 | 244 | 12 |
| *%* | | | *54.4* | *45.6* | *71.1* | *27.6* | *1.4* |
| 20 ≤ BMI < 25 | 2221 | 43.6 | 1285 | 936 | 1344 | 829 | 48 |
| *%* | | | *57.9* | *42.1* | *60.5* | *37.3* | *2.2* |
| 25 ≤ BMI < 30 | 1523 | 29.9 | 890 | 633 | 627 | 867 | 29 |
| *%* | | | *58.4* | *41.6* | *41.2* | *56.9* | *1.9* |
| BMI ≥ 30 | 471 | 9.2 | 265 | 206 | 188 | 270 | 13 |
| *%* | | | *56.3* | *43.7* | *39.9* | *57.3* | *2.8* |
| **Family History** | | | | | | | |
| Yes | 1938 | 38.0 | 1111 | 827 | 786 | 1124 | 28 |
| *%* | | | *57.3* | *42.7* | *40.6* | *58.0* | *1.4* |
| No | 3162 | 62.0 | 1810 | 1352 | 2002 | 1086 | 74 |
| *%* | | | *57.2* | *42.8* | *63.3* | *34.3* | *2.3* |
| **Literacy** | | | | | | | |
| Illiterate | 1679 | 32.9 | 877 | 802 | 977 | 668 | 34 |
| *%* | | | *52.2* | *47.8* | *58.2* | *39.8* | *2.0* |
| Literate | 3421 | 67.1 | 2044 | 1377 | 1811 | 1542 | 68 |
| *%* | | | *59.7* | *40.3* | *52.9* | *45.1* | *2.0* |

**Supplementary Table 1** (cont.).

| Characteristics | **Dietary Pattern** | | **Age** | **BMI** | **Family History** | | **Literacy** | |
|---|---|---|---|---|---|---|---|---|
| | Veg. | Non-veg. | (years) | | Yes | No | Illiterate | Literate |
| **Habitat** | | | | | | | | |
| Rural | 1784 | 1137 | 21.4±3.3 | 24.2±4.3 | 1111 | 1810 | 877 | 2044 |
| *%* | *61.1* | *38.9* | | | *38.0* | *62.0* | *30.0* | *70.0* |
| Urban | 1264 | 915 | 21.5±3.3 | 24.1±4.41 | 827 | 1352 | 802 | 1377 |
| *%* | *58.0* | *42.0* | | | *38.0* | *62.0* | *36.8* | *63.2* |
| **Religion** | | | | | | | | |
| Hindu | 1808 | 980 | 20.8±3.3 | 23.2±4.1 | 786 | 2002 | 977 | 1811 |
| *%* | *64.8* | *35.2* | | | *28.2* | *71.8* | *35.0* | *65.0* |
| Sikh | 1205 | 1005 | 22.4±3.0 | 25.3±4.3 | 1124 | 1086 | 668 | 1542 |
| *%* | *54.5* | *45.5* | | | *50.9* | *49.1* | *30.2* | *69.8* |
| Others | 35 | 67 | 20.3±3.4 | 24.4±4.8 | 28 | 74 | 34 | 68 |
| *%* | *34.3* | *65.7* | | | *27.5* | *72.5* | *33.3* | *66.7* |
| **Dietary Pattern** | | | | | | | | |
| Vegetarian | | | 21.9±3.2 | 24.5±4.3 | 1249 | 1799 | 959 | 2089 |
| *%* | | | | | *41.0* | *59.0* | *31.5* | *68.5* |
| Non-vegetarian | | | 21 ±3.3 | 23.8±4.2 | 689 | 1363 | 720 | 1332 |
| *%* | | | | | *33.6* | *66.4* | *35.1* | *64.9* |
| **Age (years)** | | | | | | | | |
| Age ≤ 20 | 1062 | 1006 | | 22.7±3.9 | 440 | 1628 | 793 | 1275 |
| *%* | *51.4* | *48.6* | | | *21.3* | *78.7* | *38.3* | *61.7* |
| 20 < age ≤ 25 | 1585 | 863 | | 25.0±4.3 | 1151 | 1297 | 691 | 1757 |
| *%* | *64.7* | *35.3* | | | *47.0* | *53.0* | *28.2* | *71.8* |
| 25 < age ≤ 30 | 374 | 166 | | 26.1±4.4 | 322 | 218 | 182 | 358 |
| *%* | *69.3* | *30.7* | | | *59.6* | *40.4* | *33.7* | *66.3* |
| Age > 30 | 27 | 17 | | 27.2±4.6 | 25 | 19 | 13 | 31 |
| *%* | *61.4* | *38.6* | | | *56.8* | *43.2* | *29.5* | *70.5* |
| **BMI** | | | | | | | | |
| BMI < 20 | 473 | 412 | 20.1±3.1 | | 114 | 771 | 324 | 561 |
| *%* | *53.4* | *46.6* | | | *12.9* | *87.1* | *36.6* | *63.4* |
| 20 ≤ BMI < 25 | 1299 | 922 | 21.0±3.2 | | 598 | 1623 | 787 | 1434 |
| *%* | *58.5* | *41.5* | | | *26.9* | *73.1* | *35.4* | *64.6* |
| 25 ≤ BMI < 30 | 959 | 564 | 22.3±3.1 | | 904 | 619 | 431 | 1092 |
| *%* | *63.0* | *37.0* | | | *59.4* | *40.6* | *28.3* | *71.7* |
| BMI ≥ 30 | 317 | 154 | 23 ±3.2 | | 322 | 149 | 137 | 334 |
| *%* | *67.3* | *32.7* | | | *68.4* | *31.6* | *29.1* | *70.9* |
| **Family History** | | | | | | | | |
| Yes | 1249 | 689 | 22.7±3.0 | 26.4±4.1 | | | 458 | 1480 |
| *%* | *64.4* | *35.6* | | | | | *23.6* | *76.4* |
| No | 1799 | 1363 | 20.8±3.2 | 22.9±3.9 | | | 1221 | 1941 |
| *%* | *56.9* | *43.1* | | | | | *38.6* | *61.4* |
| **Literacy** | | | | | | | | |
| Illiterate | 959 | 720 | 21.0±3.4 | 23.8±4.3 | 458 | 1221 | | |
| *%* | *57.1* | *42.9* | | | *27.3* | *72.7* | | |
| Literate | 2089 | 1332 | 21.7±3.2 | 24.4±4.3 | 1480 | 1941 | | |
| *%* | *61.1* | *38.9* | | | *43.3* | *56.7* | | |

**Supplementary Table 2.** Prevalence (%) of GDM according to GDM diagnostic criteria and to components of the GDM definition (unadjusted data).

| | ***FPG*** | | ***2-h PG*** | |
|---|---|---|---|---|
| | **FPG ≥5.1** (mmol/l) (N=1679) | **FPG ≥7.0** (mmol/l) (N=52) | ***2-h PG* ≥7.8** (mmol/l) (N=438) | ***2-h PG* ≥8.5** (mmol/l) (N=229) |
| **Overall prevalence (%)** | 32.9 | 1.0 | 8.6 | 4.5 |
| **Prevalence of GDM according to risk factor (%)** | | | | |
| **Habitat** | | | | |
| Rural | 30.4* | 1.1 | 7.5* | 3.6* |
| Urban | 36.3 | 1.0 | 10.1 | 5.6 |
| **Religion** | | | | |
| Hindu | 32.0 | 1.1 | 9.4* | 5.1* |
| Sikh | 34.0 | 1.0 | 7.4 | 3.7 |
| Others | 34.3 | 0.0 | 12.6 | 6.9 |
| **Diet** | | | | |
| Vegetarian | 34.7 | 1.1* | 7.6* | 3.8* |
| Non-vegetarian | 30.4 | 1.0 | 10.1 | 5.5 |
| **Age (years)** | | | | |
| Age ≤ 20 | 29.8* | 0.9 | 8.2 | 4.4 |
| 20 < age ≤ 25 | 34.3 | 1.1 | 8.8 | 4.8 |
| 25 < age ≤ 30 | 38.2 | 0.9 | 8.9 | 3.2 |
| Age > 30 | 40.9 | 2.3 | 11.4 | 9.1 |
| **BMI (kg/m$^2$)** | | | | |
| BMI < 20 | 30.9 | 0.7 | 8.3 | 4.3 |
| 20 ≤ BMI < 25 | 31.9 | 0.8 | 8.7 | 4.7 |
| 25 ≤ BMI < 30 | 34.6 | 1.4 | 7.8 | 3.9 |
| BMI ≥ 30 | 36.1 | 1.3 | 11.3 | 5.7 |
| **Family History** | | | | |
| Yes | 33.8 | 1.0 | 8.8 | 4.0 |
| No | 32.4 | 1.0 | 8.5 | 4.8 |
| **Literacy** | | | | |
| Illiterate | 33.5 | 1.0 | 11.0* | 6.0* |
| Literate | 32.6 | 1.0 | 7.4 | 3.7 |

*Significant difference $P \leq 0.05$ (Pearson chi2 test)

# Paper II

**DIABETIC**Medicine

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# Research: Pregnancy

# Insulin secretion and action in North Indian women during pregnancy

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## Abstract

**Aim** The relative roles(s) of impaired insulin secretion vs. insulin resistance in the development of gestational diabetes mellitus depend upon multiple risk factors and diagnostic criteria. Here, we explored their relative contribution to gestational diabetes as defined by the WHO 1999 (GDM1999) and adapted WHO 2013 (GDM2013) criteria, excluding the 1-h glucose value, in a high-risk Indian population from Punjab.

**Methods** Insulin secretion (HOMA2-B) and insulin action (HOMA2-IR) were assessed in 4665 Indian women with or without gestational diabetes defined by the GDM1999 or adapted GDM2013 criteria.

**Results** Gestational diabetes defined using both criteria was associated with decreased insulin secretion compared with pregnant women with normal glucose tolerance. Women with gestational diabetes defined by the adapted GDM2013, but not GDM1999 criteria, were more insulin resistant than pregnant women with normal glucose tolerance, and furthermore displayed lower insulin secretion than GDM1999 women. Urban habitat, illiteracy, high age and low BMI were independently associated with reduced insulin secretion, whereas Sikh religion, increasing age and BMI, as well as a family history of diabetes were independently associated with increased insulin resistance.

**Conclusions** Gestational diabetes risk factors influence insulin secretion and action in North Indian women in a differential manner. Gestational diabetes classified using the adapted GDM2013 compared with GDM1999 criteria is associated with more severe impairments of insulin secretion and action.

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## Introduction

Gestational diabetes mellitus defines newly diagnosed hyperglycaemia/diabetes in pregnancy [1], and is associated with increased pregnancy complications, as well as an increased risk of developing Type 2 diabetes later in life for both mother and offspring [1,2]. However, the plasma glucose cut-off levels defining gestational diabetes remains controversial, and our understanding of its underlying pathophysiological mechanisms is incomplete. The World Health Organization (WHO) 2013 criteria were introduced to diagnose and treat gestational diabetes earlier and thereby reduce maternal and fetal complications [3]. Lowering the fasting plasma glucose cut-off level from > 7.0 to > 5.1 mmol/L was associated with a threefold increase in gestational diabetes among North Indian women [4], but it is not known whether it performed better in terms of detecting more complications. Also, the extent to which the underlying pathophysiological mechanisms may differ in women diagnosed by the WHO1999 (GDM1999) or WHO2013 (GDM2013) criteria is unknown.

The main determinants of glucose levels are insulin secretion and insulin action, and studies have shown that women with GDM1999 exhibit both impaired insulin secretion and action [5,6]. The relative contribution of defects in insulin secretion and action is, however, masked by physiological insulin resistance during the last trimester of pregnancy [7]. We are unaware of any comparisons of the role of impaired insulin secretion vs. insulin resistance in women with gestational diabetes using the GDM1999 vs. the GDM2013 criteria.

To address the relative contribution of defects in insulin secretion and action in the development of gestational diabetes defined using either the 1999 or adapted 2013

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**What's new?**

- North Indian women with gestational diabetes diagnosed with both the WHO 1999 (GDM1999) and adapted WHO 2013 (GDM2013; excluding the 1-h glucose value) criteria are characterized by impaired insulin secretion.
- Women with gestational diabetes are characterized by insulin resistance only when diagnosed with the adapted GDM2013 criteria.
- Risk factors for gestational diabetes in North Indian women influence insulin secretion and action in pregnancy in a differential manner.

diagnostic criteria (excluding 1-h glucose) we studied 4665 North Indian women between gestational weeks 24 and 28.

## Patients and methods

In total, 5100 women were randomly selected when visiting antenatal care units in rural and urban areas of Punjab in North India [4]. The study was approved by the ethics committee (reg. no. ECR/525/Inst/PB/2014) and the Directorate of Medical Education and Research, Punjab, India.

Details of the selection and study procedures for the current cohort were published previously [4]. The women were interviewed about age, residence (rural/urban), education (literate/illiterate), religion, diet (vegetarianism), family history of diabetes (first- and second-degree relatives), obstetric history, age at marriage and use of medication. Weight and height were measured, and BMI calculated.

A fasting venous blood sample was drawn for glucose measurements using the glucose oxidase peroxidase method. Fasting insulin concentrations were measured by enzyme-linked immunosorbent assay (ELISA; insulin ELISA kit, Diametra, Milan, Italy) [4]. A 75-g oral glucose tolerance test (OGTT) was performed and to avoid the discomfort of a venous cannula, 2-h capillary blood glucose was measured using a glucometer (Accu-Chek, Roche Diagnostics, Mumbai, India) [4]. A correction factor of 0.85 was applied to transform capillary into venous glucose concentrations [4,8].

Beta-cell function (HOMA2-B) and insulin resistance (HOMA2-IR) were determined using the HOMA2 calculator [9]. Gestational diabetes was diagnosed using WHO 1999 (fasting plasma glucose $\geq$ 7.0 mmol/L and/or 2-h glucose $\geq$ 7.8 mmol/L) and the adapted WHO 2013 (fasting plasma glucose $\geq$ 5.1 mmol/L and/or 2-h glucose $\geq$ 8.5 mmol/L) criteria [4].

## Statistics

Student's *t*-tests were used to compare mean values between women with and without gestational diabetes, and analysis of variance (ANOVA) for multiple comparisons between variables. A *z*-test was used for comparisons within and between groups. Linear regression analysis, adjusted for independent variables was used to test the influence of risk factors on HOMA2-IR and HOMA2-B. A *P*-value of $\leq 0.05$ was considered statistically significant. Analyses were performed using SPSS software v. 20.0 (IBM, NY, USA).

## Results

### Clinical characteristics

In total, 4665 women (91.5%) underwent an OGTT. The characteristics are shown in Table 1. Age was significantly higher in gestational diabetes compared with pregnant women with normal glucose tolerance using the adapted GDM2013 criteria ($P \leq 0.001$). Women with gestational diabetes by both criteria were shorter than those with normal glucose tolerance ($P = 0.001$ and 0.008). Fasting glucose levels were higher in GDM2013 than in GDM1999 women ($P \leq 0.001$), whereas the opposite was true for the 2-h glucose levels ($P = 0.001$). Women with gestational diabetes had lower HOMA2-B than those with normal glucose tolerance using both criteria (all $P \leq 0.001$), but HOMA2-IR was significantly higher in gestational diabetes than in women with normal glucose tolerance using adapted GDM2013 criteria ($P \leq 0.001$, adjusted $P = 0.008$).

### Factors influencing insulin secretion and action

Women from urban areas displayed lower HOMA2-B ($P \leq 0.001$) and HOMA2-IR ($P = 0.01$) than rural women (Table 2), and the same was seen for Hindu women who had lower HOMA2-B and HOMA2-IR than Sikh women ($P \leq 0.001$). Women who were illiterate had lower HOMA2-B ($P = 0.002$) and were more insulin sensitive (HOMA2-IR) than those who were literate ($P = 0.002$). Diet did not influence HOMA2-B or HOMA2-IR. Ageing had a strong effect on HOMA2-IR ($P \leq 0.001$), but little or no effect on HOMA2-B ($P = 0.06$). Expectedly, increasing BMI was associated with insulin resistance, i.e. higher HOMA2-IR ($P \leq 0.001$). Family history of diabetes was associated with higher HOMA2-IR ($P \leq 0.001$) with no effect on HOMA2-B ($P = 0.76$). Mean HOMA2-B and HOMA2-IR in relation to subject characteristics and environmental factors in women meeting the GDM1999 and adapted GDM2013 criteria are shown in Table S1.

## Discussion

The key findings of this study were that North Indian women diagnosed with gestational diabetes using GDM1999 or adapted GDM2013 criteria, showed impaired insulin secretion compared with pregnant women with normal glucose

**Table 1** Clinical characteristic of pregnant women categorized as having gestational diabetes or pregnant women with normal glucose tolerance using the WHO 1999 (GDM1999) or the adapted WHO 2013 (GDM2013) criteria. The statistical comparisons between groups are uncorrected for confounding variables

| | GDM1999 | | | Adapted GDM2013 | | | GDM1999 vs. adapted GDM2013 | |
|---|---|---|---|---|---|---|---|---|
| | FPG ≥ 7.0 or 2-h PG ≥ 7.8 mmol/L | | | FPG ≥ 5.1 or 2-h PG ≥ 8.5 mmol/L | | | GDM | Pregnant normal glucose tolerance |
| | Gestational diabetes ($n$ = 405) | Pregnant normal glucose tolerance ($n$ = 4260) | $P$-value | Gestational diabetes ($n$ = 1618) | Pregnant normal glucose tolerance ($n$ = 3047) | $P$-value | $P$-value | $P$-value |
| Age (years) | 21.0 (20.0; 23.0) | 21.0 (19.0; 23.5) | 0.91 | 21.0 (20.0; 24.0) | 21.0 (19.0; 23.0) | ≤ 0.001 | 0.13 | 0.06 |
| Height (cm) | 143 (133; 154) | 148 (135; 162) | 0.001 | 146 (134; 160) | 149 (134; 163) | 0.008 | 0.05 | 0.55 |
| BMI (kg/m$^2$) | 23.8 (21.0; 27.4) | 23.8 (20.9; 27.1) | 0.34 | 23.8 (21.1; 27.4) | 23.7 (20.8; 26.9) | 0.02 | 0.96 | 0.37 |
| Fasting plasma glucose (mmol/L) | 5.33 (4.72; 6.05) | 4.77 (4.38; 5.16) | ≤ 0.001 | 5.38 (5.22; 5.61) | 4.50 (4.22; 4.83) | ≤ 0.001 | ≤0.001 | ≤ 0.001 |
| 2-h plasma glucose (mmol/L) | 8.49 (8.02; 9.53) | 6.04 (5.24; 6.70) | ≤ 0.001 | 6.61 (5.80; 7.36) | 5.94 (5.19; 6.65) | ≤ 0.001 | ≤0.001 | 0.001 |
| Fasting plasma insulin (pmol/L) | 5.8 (4.7; 7.7) | 6.1 (4.7; 8.3) | 0.15 | 6.0 (4.8; 8.4) | 6.1 (4.7; 8.2) | 0.71 | 0.17 | 0.66 |
| HOMA2-B | 71.7 (54.2; 96.8) | 92.5 (71.6; 123.8) | ≤ 0.001 | 69.1 (55.4; 87.1) | 103.3 (82.4; 136.0) | ≤ 0.001 | 0.15 | ≤ 0.001 |
| HOMA2-B adjusted* | 75.5 (54.8–101.5) | 93.3 (72.0–125.2) | ≤ 0.001 | 70.0 (56.0–89.6) | 104.7 (83.9–136.4) | ≤ 0.001 | 0.04 | ≤ 0.001 |
| HOMA2-IR | 0.76 (0.62–1.02) | 0.78 (0.60–1.06) | 0.85 | 0.80 (0.64–1.11) | 0.77 (0.59–1.04) | ≤ 0.001 | 0.07 | 0.04 |
| HOMA2-IR adjusted* | 0.83 (0.64–1.06) | 0.82 (0.61–1.10) | 0.70 | 0.84 (0.64–1.13) | 0.81 (0.61–1.08) | 0.008 | 0.52 | 0.27 |

Data are median (25th; 75th percentile).
*Adjusted for habitat, religion, diet, age, height, BMI, family history of diabetes and literacy.
FPG, fasting plasma glucose; PG, plasma glucose.

**Table 2** Mean HOMA2-B and HOMA2-IR in relation to subject characteristics and environmental factors

| Characteristics | *n* (%) | HOMA2-B | *P*-value | HOMA2-IR | *P*-value |
|---|---|---|---|---|---|
| Total | 4665 (100) | 90.3 (70.0; 121.7) | | 0.78 (0.60; 1.06) | |
| Residence | | | ≤ 0.001 | | 0.01 |
| Rural | 2687 (57.60) | 93.3 (71.7; 125.6) | | 0.79 (0.61; 1.07) | |
| Urban | 1978 (42.40) | 87.2 (67.4; 116.7) | | 0.76 (0.60; 1.02) | |
| Religion | | | ≤ 0.001 | | ≤ 0.001 |
| Hindu | 2530 (54.23) | 88.3 (69.2; 116.0) | | 0.74 (0.58; 0.97) | |
| Sikh | 2044 (43.82) | 93.9 (70.9; 132.7) | | 0.83 (0.63; 1.19) | |
| Other | 91 (1.95) | 89.0 (64.6; 115.8) | | 0.74 (0.55; 0.96) | |
| Diet | | | 0.38 | | 0.21 |
| Vegetarian | 2665 (57.13) | 89.6 (70.1; 120.7) | | 0.78 (0.61; 1.06) | |
| Non-vegetarian | 2000 (42.87) | 91.7 (69.6; 123.7) | | 0.77 (0.60; 1.04) | |
| Age (years) | | | 0.06 | | ≤ 0.001 |
| ≤ 20 | 1893 (40.58) | 89.0 (69.3; 118.8) | | 0.73 (0.58; 0.96) | |
| 20 to ≤ 25 | 2244 (48.10) | 92.5 (70.9; 125.1) | | 0.81 (0.62; 1.14) | |
| 25 to ≤ 30 | 488 (10.46) | 88.5 (67.6; 120.7) | | 0.80 (0.65; 1.17) | |
| > 30 | 40 (0.86) | 87.2 (68.2; 124.9) | | 1.00 (0.66; 1.42) | |
| BMI (kg/m$^2$) | | | ≤ 0.001 | | ≤ 0.001 |
| < 20 | 799 (17.13) | 87.2 (68.7; 112.8) | | 0.73 (0.59; 0.94) | |
| 20 to < 25 | 2040 (43.73) | 88.5 (69.1; 118.5) | | 0.75 (0.59; 0.99) | |
| 25 to < 30 | 1394 (29.88) | 94.3 (71.2; 130.2) | | 0.82 (0.62; 1.20) | |
| ≥ 30 | 432 (9.26) | 99.9 (72.4; 143.2) | | 0.92 (0.69; 1.48) | |
| Family history | | | 0.76 | | ≤ 0.001 |
| Yes | 1783 (38.22) | 89.1 (68.8; 123.8) | | 0.81 (0.61; 1.17) | |
| No | 2882 (61.78) | 91.1 (70.4; 121.0) | | 0.76 (0.60; 1.01) | |
| Literacy | | | 0.002 | | 0.002 |
| Illiterate | 1509 (32.35) | 88.3 (69.5; 114.2) | | 0.76 (0.59; 1.02) | |
| Literate | 3156 (67.65) | 91.7 (70.0; 125.9) | | 0.79 (0.61; 1.08) | |

Data are median (25th; 75th percentile). Overall *P*-values are determined by Kruskal–Wallis equality of populations rank test. Applying a post-hoc test (Dunn's) with Sidak correction, significant differences were found between the following categories: HOMA2-B, $P \leq 0.001$, (Hindu and Sikh), (BMI < 20 and 25 to < 30), (BMI < 20 and ≥ 30), (BMI 20 to < 25 and 25 to < 30), (BMI 20 to < 25 and ≥ 30); HOMA2-IR, $P \leq 0.001$: (Hindu and Sikh), (age ≤ 20 and 20 to ≤ 25), (age ≤ 20 and 25 to ≤ 30), (age ≤ 20 and > 30), (BMI < 20 and 25 to < 30), (BMI < 20 and ≥ 30), (20 to < 25 and 25 to < 30), (BMI 20 to < 25 and ≥ 30), (BMI 25 to < 30 and ≥ 30), $P \leq 0.01$, (Sikh and others).

tolerance. In addition, when diagnosed with the adapted 2013 criteria, women with gestational diabetes were more insulin resistant than pregnant women who were glucose tolerant. Notably, established environmental risk factors for gestational diabetes influenced insulin resistance and insulin secretion differently in North Indian women.

The finding of more severe impairment in insulin secretion using adapted GDM2013 compared with GDM1999 criteria is in agreement with those of Noctor *et al*. [10] suggesting a less-favourable metabolic profile in women meeting the GDM2013 criteria compared with those meeting GDM1999 criteria [10].

By contrast, pregnant women with normal glucose tolerance according to the adapted 2013 criteria appeared metabolically healthier than women classified using the 1999 criteria (Table 1). The extent to which this influences the risk of short- and long-term pregnancy complications in mother and offspring of pregnancies classified using the different criteria requires further study.

Despite the higher cut-off level for fasting plasma glucose of 7.0 mmol/L (GDM1999) compared with 5.1 mmol/L (GDM2013), the average fasting plasma glucose level in GDM1999 women was slightly lower than in women diagnosed using the adapted GDM2013 criteria. One explanation for this is that it is a corollary of lower 2-h plasma glucose in GDM2013. The majority of the women classified using the adapted GDM2013 criteria qualified for a diagnosis of gestational diabetes because of elevated fasting plasma glucose ($n = 1779$), whereas for the GDM1999 criteria women qualified based on elevated 2-h glucose ($n = 458$) [4]. This difference may explain the lower insulin secretion in adapted GDM2013 compared with GDM1999 cases.

Not surprisingly, increased BMI and age were associated with increased insulin resistance and with a (possibly compensatory) increased insulin secretion until age 30 years, after which insulin secretion declined (Table 2). This supports the notion of a general decline in β-cell function with age [11], potentially due to the failure of pancreatic β-cells to compensate for age-related insulin resistance.

A family history of diabetes was exclusively associated with insulin resistance. This is consistent with findings from first-degree relatives of patients with Type 2 diabetes [12], but in contrast to genome-wide association studies showing that most Type 2 diabetes-associated single nucleotide polymorphisms affect insulin secretion rather than insulin action [13].

The reason for the difference in insulin secretion between Sikh and Hindu women is not known, but may be due to unknown differences in lifestyle and/or genetics. Hindus are more often vegetarians than Sikhs. However, vegetarian diet

 

did not influence insulin secretion or action in this study (Table 2), therefore other unknown factors may play a role.

Illiteracy, a proxy for education and social status, has been associated with an increased risk of gestational diabetes [14]. Here, illiteracy was associated with impaired insulin secretion, possibly reflecting inadequate nutrition and early growth. The relatively higher insulin sensitivity associated with illiteracy may be due to lower body fat mass.

HOMA has been used previously for the assessment of both insulin secretion and action in gestational diabetes [15]. The current data show that the majority of suspected and investigated gestational diabetes risk factors in North Indian women primarily operate by influencing *in vivo* insulin resistance.

Limitations of this study include multiple comparisons with *P*-values unadjusted for multiple testing (Table 2). Furthermore, there are potential sources of bias related to the validity of the recorded gestational diabetes risk factor assessments in India, including illiteracy [16]. The lack of a 1-h glucose sample during the OGTT is another potential limitation. However Chinese women diagnosed using the GDM2013 criteria had significantly higher 1-h glucose concentrations than women diagnosis using the GDM1999 criteria [17]. Thus, the much higher number of women with gestational diabetes identified using the adapted GDM2013 vs. GDM1999 criteria in this study is unlikely to have been lower if 1-h OGTT plasma glucose levels were available, supporting the validity of the current data. Indeed, the reported HOMA data are calculated entirely from fasting plasma glucose and insulin levels.

In conclusion, North Indian women with gestational diabetes defined by both GDM1999 and adapted GDM2013 criteria are characterized by impaired insulin secretion, but only when classified using the adapted GDM2013 criteria by insulin resistance. Further investigations into the interaction between genetic and lifestyle factors predisposing to gestational diabetes in North Indian women compared with women of other ethnic origin should be prioritized.

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#### Competing interests

CB is a stockholder in Novo Nordisk A/S and AV is employed by AstraZeneca. No other conflict of interest is declared.

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#### Author contributions

GPA, CB and RBP designed the study, acquired data, analysed and interpreted data, and drafted the manuscript. RGT and AP interpreted the data and drafted the manuscript. PA and RBP performed statistical analyses. RBP, LCG and AAV designed the study, interpreted data and drafted the manuscript. All authors have approved the final version of the manuscript to be published.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Mean HOMA2-B and HOMA2-IR in relation to subject characteristics and environmental factors in women meeting the GDM1999 and adapted GDM2013 criteria.

 

# Insulin Secretion and Action in North Indian Women during Pregnancy

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**Table S1.** Mean HOMA2-B and HOMA2-IR in relation to subject characteristics and environmental factors in women meeting the GDM1999 and the adapted GDM2013 criteria.

| | GDM1999 (FPG ≥7.0 or 2-hr PG ≥7.8 mmol/l) | | | | | Adapted GDM2013 (FPG ≥5.1 or 2-hr PG ≥8.5 mmol/l) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Characteristics | n (%) | HOMA2-B | *p-value* | HOMA2-IR | *p-value* | n (%) | HOMA2-B | *p-value* | HOMA2-IR | *p-value* |
| Total | 405(100) | 71.70 (54.15;97.20) | | 0.76 (0.62;1.02) | | 1618(100) | 69.1 (55.37;87.1) | | 0.80 (0.64;1.11) | |
| Habitat | | | *0.038* | | *0.12* | | | *≤0.001* | | *≤0.01* |
| Rural | 201 (49.63) | 69.0 (51.65;92.80) | | 0.72 (0.60;1.00) | | 861 (53.21) | 70.8 (57.3;88.8) | | 0.82 (0.65;1.14) | |
| Urban | 204 (50.37) | 78.35 (56.6;104.85) | | 0.78 (0.63;1.05) | | 757 (46.79) | 67.0 (53.45;83.70) | | 0.77 (0.63;1.03) | |
| Religion | | | *>0.05* | | *0.023* | | | *≤0.001* | | *≤0.001* |
| Hindu | 241 (59.51) | 73.80 (57.1;97.65) | | 0.74 (0.60;1.00) | | 866 (53.52) | 67.60 (53.40;85.23) | | 0.77 (0.62;1.02) | |
| Sikh | 153 (37.78) | 70.30 (50.75;96.25) | | 0.80 (0.66;1.12) | | 720 (44.50) | 70.90 (57.70;91.10) | | 0.84 (0.66;1.21) | |
| Others | 11 (2.71) | 65.10 (51.30;101.80) | | 0.71 (0.57;0.91) | | 32 (1.98) | 64.70 (51.40;83.78) | | 0.73 (0.56;1.06) | |
| Diet | | | *0.28* | | *0.053* | | | *0.08* | | *0.002* |
| Vegetarian | 216 (53.33) | 71.10 (51.20;96.30) | | 0.79 (0.62;1.11) | | 961 (59.39) | 70.00 (55.70;88.20) | | 0.82 (0.66;1.14) | |
| Non-Vegetarian | 189 (46.67) | 72.00 (57.20;101.85) | | 0.72 (0.60;1.00) | | 657 (40.61) | 67.60 (54.90;84.75) | | 0.77 (0.62;1.04) | |
| Age (years) | | | *0.17* | | *0.017* | | | *0.001* | | *≤0.001* |
| Age ≤ 20 | 152 (37.53) | 69.30 (55.13;91.40) | | 0.70 (0.59;0.98) | | 592 (36.59) | 65.85 (55.00;81.75) | | 0.76 (0.62;1.00) | |
| 20 < age ≤ 25 | 206 (50.86) | 78.90 (55.35;104.78) | | 0.80 (0.63:1.07) | | 812 (50.19) | 71.45 (56.03;90.55) | | 0.82 (0.65;1.17) | |
| 25 < age ≤ 30 | 43 (10.62) | 64.60 (47.80;93.50) | | 0.83 (0.66;1.21) | | 196 (12.11) | 67.90 (54.15;90.68) | | 0.82 (0.67;1.17) | |
| Age > 30 | 4 (0.99) | 64.70 (48.20;83.45) | | 1.11 (0.56;1.28) | | 18 (1.11) | 73.50 (60.38;102.73) | | 1.06 (0.66;1.41) | |
| BMI (kg/m$^2$) | | | *0.078* | | *0.032* | | | *≤0.001* | | *≤0.001* |
| BMI < 20 | 68 (16.79) | 78.60 (54.50;95.80) | | 0.70 (0.56;0.98) | | 261 (16.13) | 66.70 (55.30;81.30) | | 0.77 (0.62;0.99) | |
| 20 ≤ BMI < 25 | 177 (43.70) | 73.70 (57.70;96.65) | | 0.76 (0.63;0.98) | | 694 (42.89) | 67.10 (54.30;83.55) | | 0.76 (0.63;1.02) | |
| 25 ≤ BMI < 30 | 111 (27.41) | 61.20 (47.00; 96.50) | | 0.77 (0.62;1.11) | | 498 (30.78) | 71.70 (55.63;93.20) | | 0.83 (0.65;1.22) | |
| BMI ≥ 30 | 49 (12.1) | 73.80 (58.20;115.10) | | 0.93 (0.64;1.31) | | 165 (10.20) | 75.20 (59.20;106.55) | | 0.95 (0.74;1.52) | |
| Family history | | | *0.91* | | *0.23* | | | *0.024* | | *0.083* |
| Yes | 155 (38.27) | 72.00 (51.50;105.00) | | 0.77 (0.62;1.15) | | 636 (39.31) | 70.40 (56.43;91.30) | | 0.82 (0.63;1.20) | |
| No | 250 (61.73) | 71.45 (55.20;95.28) | | 0.76 (0.61;1.00) | | 982 (60.69) | 67.95 (55.00;85.33) | | 0.79 (0.64;1.06) | |
| Literacy | | | *0.99* | | *0.13* | | | *0.66* | | *0.77* |
| Illiterate | 164 (40.49) | 74.20 (57.78;98.98) | | 0.76 (0.63;1.01) | | 544 (33.62) | 68.80 (55.55;85.90) | | 0.80 (0.65;1.11) | |
| Literate | 241 (59.51) | 70.00 (51.30;95.60) | | 0.76 (0.61; 1.05) | | 1074 (66.38) | 69.15 (55.28;87.80) | | 0.80 (0.63;1.11) | |

Data are median ($25^{th}$;$75^{th}$ percentile)

Overall *p*-values are determined by Kruskal-Wallis equality of *p*opulations rank test.

Applying a post-hoc test (Dunn's) with Sidak correction, significant differences were found between the following categories:

*HOMA2-B:* $P \leq 0.001$: (Hindu and Sikh), (BMI<20 and 25≤BMI<30), (BMI<20 and BMI≥30), (20≤BMI<25 and 25≤BMI<30), (20≤BMI<25 and BMI≥30).

*HOMA2-IR:* $P \leq 0.001$: (Hindu and Sikh), (Age≤20 and 20<age≤25), (Age≤20 and 25<age≤30), (Age≤20 and Age>30), (BMI<20 and 25≤BMI<30), (BMI<20 and BMI≥30), (20≤BMI<25 and 25≤BMI<30), (20≤BMI<25 and BMI≥30), (25≤BMI<30 and BMI≥30). $P \leq 0.01$: (Sikh and Others).

# Paper III

# Association between genetic risk variants and glucose intolerance during pregnancy in North Indian women

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## Abstract

**Objective**: Gestational diabetes (GDM) is a more common problem in India than in many other parts of the world but it is not known whether this is due to unique environmental factors or a unique genetic background. To address this question we examined whether the same genetic variants associated with GDM and type 2 Diabetes (T2D) in Caucasians also were associated with GDM in North Indian women.

**Material and Methods**: 5100 pregnant women of gestational age 24-28 weeks from Punjab were studied by a 75g oral glucose tolerance test (OGTT). GDM was diagnosed by both WHO 1999 and 2013 criteria. 79 SNPs previously associated with T2D and glycemic traits (12 of them also with GDM) were genotyped on a Sequenom platform and using Taqman assays.

**Results:** In general, there were stronger genetic associations with GDM defined by 1999 than by 2013 criteria. In support of previous findings in Caucasian GDM, SNPs in the *KCJN11* and *GRB14* were associated with risk of GDM 1999 in these Indian women (both p=0.02). Several SNPs were associated with glucose and insulin values. Notably, T2D risk alleles of the variant rs1552224 near *CENTD2,* rs11708067 in *ADCY5* and rs11605924 in *CRY2* genes were associated with protection from GDM regardless of criteria ($p<0.025$). rs7607980 near *COBLL1* ($p = 0.0001$), rs13389219 near GRB14 (0.026) and rs10423928 in GIPR( $p = 0.012$) associated with insulin resistance. The risk allele (rs7903146) in the *TCF7L2* gene showing the strongest association in general with T2D was significantly associated with GDM only by applying the most stringent interpretation of WHO criteria.

**Conclusion:** GDM in women from Punjab in Northern India shows a clear genetic component, which is mostly shared with GDM in other parts of the world. Interestingly some T2D risk variants were in fact protective for GDM in these Indian women.

## Introduction

Gestational Diabetes Mellitus (GDM) has been officially defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy [1-3] irrespective of treatment and whether or not the condition persists after pregnancy. GDM represents almost 90% of all pregnancies complicated by diabetes [4]. Evidence suggests that prevalence of GDM is rapidly increasing, ranging from 2-14% depending upon diagnostic criteria [5, 6]. In a study on South Indian women, GDM prevalence varied between 12-21% [7] while another study on North Indian women reported a prevalence of 10% using WHO criteria [8]. The hallmark of GDM is increased insulin resistance accompanied by decreased compensatory insulin secretory response. Type 2 diabetes (T2D) is caused by increased insulin resistance and decreased insulin secretion to compensate for the former. Thus, both T2D and GDM share the same pathophysiology. Both are influenced by similar risk factors like high BMI, history of abnormal glucose intolerance, family history of diabetes mellitus, age, and ethnicity [9-11].

Family history of diabetes, both T2D and GDM is known to increase GDM risk, indicative of a common genetic component underlying both T2D and GDM [12, 13]. Till date, more than 120 T2D risk loci have been positively confirmed in association with T2D [14]. A large proportion of them has shown association with GDM risk in genome wide association studies (GWAS) and candidate gene studies. T2D risk variants at *MTNR1B, FTO, TLE1, G6PC2, GCKR, TCF7L2, ADCY5, CDKAL1, TCF2, HNF1B, PPARG, KCNJ11, SLC30A8* have previously been shown to associate with GDM risk in European populations [15-18] whereas variants in *CDKAL1* and *CDKN2A/2B, MTNR1* and *KCNQ1* were associated with GDM in Korean women [19, 20].

Some genetic variants are more specific for Asian Indian patients with T2D, e.g. in the *SGCG* (rs9552911) and *TMEM163* (rs998451) genes [21-25]. However, the genetic basis of GDM in India is vastly unexplored. SNPs rs7754840 and rs7756992 in the *CDKAL1* gene were found to be associated with GDM in South Indian women [26]. In another recent study, variants in the *HMG20A* (rs7178572) and *HNF4A* (rs4812829) genes were associated with GDM and T2DM in India [27]. The aim of the present study was to investigate whether these known variants associated with

GDM and T2D in Indian and European populations are associated with GDM in Punjabi women.

## Materials and Methods

### Study Population and phenotyping

The subjects for the study were recruited by applying a multistage random technique for screening a representative group of 5100 pregnant women in the State of Punjab in North India for GDM (Gestational Diabetes Mellitus). All pregnant women during gestational week 24-28 weeks in the region were recruited [8]. Questionnaire included BMI, family history of diabetes, diet, age, habitat (urban &rural), educational status and religion. Glucose was measured in venous plasma samples at fasting and 2 hours after a 75 g glucose challenge using glucometers (Accucheck-Roche Diagnostics). A 75 g oral glucose tolerance test (OGTT) was performed at all sites. Also fasting insulin levels were measured. All information material and written consent forms in 3 languages (Hindi, Punjabi & English) were duly signed by the subjects and the study approval by local Ethical Committees. The fasting plasma insulin concentrations were determined with ELISA (Diametra, Milan, Italy; intra- and inter-assay variation of <5.0% and <10.0%, respectively)**.** The homeostatic model assessment (HOMA2) was used to quantify insulin resistance (HOMA2-IR) and beta-cell function (HOMA2-B) from fasting insulin and glucose values using the HOMA2 calculator v2.2.3 (http://www.dtu.ox.ac.uk/homacalculator/) [28]. The clinical characteristics of subjects are shown in Table 1**.**

### Genotyping

DNA was extracted from frozen and stored buffy coats using (QIAGEN Autopure LS kits. Six SNPs previously associated with GDM or T2D in India [21, 22, 26, 27, 29] (supplementary table 1) and 79 SNPs previously associated with T2D risk in Europe and elsewhere (some of these also with GDM risk) in GWAS studies upto 2012 were selected for the present study (Supplementary table 1) [14]. Genotyping of the selected SNPs was performed on a Sequenom Mass ARRAY Platform (Sequenom San Diego, CA, USA) PLEX using MALDI-TOF mass spectrometer [30] or using Taqman allelic discrimination assays using ABI Prism 7900 sequence detection system (applied Biosystems, Foster city, CA, USA). Individuals with <60%

successful genotypes were excluded. Replication genotyping of 6% of the samples showed >98% concordance.

**Statistical analyses**

Association of selected SNPs with risk of GDM was assessed by logistic regression analysis adjusted for maternal age and BMI and results given as ORs with 95% confidence intervals (CI). We also tested for associations with fasting and 2-hour glucose fasting insulin levels as well as HOMA2-B and HOMA2-IR (Supplementary table 1) using linear regression analysis with maternal age and BMI as covariates. Data were logarithmically transformed before analysis to normalize the data for skewed distribution. For all tests, a p-value of $\leq 0.05$ was considered significant. The power to detect association with GDM2013 with 1386 GDM and 2632 controls for 79 markers at p <0,0006 (0,05/79(after Bonferroni correction) for allele frequency of 0.3 and effect size 1.3 was 0.97, which decreased to 0.64 for effects of 1.2 for the same allele frequency under an additive model. For GDM1999, with 346 GDM and 3672 controls, the corresponding figures were 0.39 and 0.12 respectively. For association with quantitative glucose traits, power to detect association was 1 at alpha 0.05 for effect allele frequency of 0.3 [31, 32].

Genetic risk scores for insulin secretion (HOMA-2B) and insulin resistance (HOMA-2IR) were also calculated.

In order to assess if different interpretations of criteria altered genetic associations, logistic regression analysis adjusting for BMI and age was performed with the GDM as outcome where GDM was defined as (i) FG $\geq$ 7.0, (ii) 2 hrG $\geq$ 7.8, (iii) FG $\geq$ 5.1, (iv) 2hrG $\geq$ 8.5 (v) FG 7.0 AND 2hrG 7.8 and (vi) FG $\geq$ 5.1 AND 2hrG $\geq$ 8.5.

All calculations were implemented in STATA.

## Results

Applying the WHO 2013 criteria resulted in a total of 1386 women with GDM (34.5 %) whereas the number was 346 (8.6%) when WHO 1999 criteria were used. Notably, only 283 (7.0%) women were diagnosed using both GDM 2013 and GDM 1999 criteria (Fig 1). We compared insulin secretion calculated as HOMA2-B and insulin resistance calculated as HOMA2-IR form the present study to those in a previously published study based on study population from the same region [33].

HOMA2-B was lower in GDM women defined by both criteria compared to pregnant normal glucose tolerant women (PNGT), and even lower compared to women with type 2 diabetes (T2D) than in GDM women (fig 2). HOMA2-IR was also higher in women with GDM compared to PNGT but lower than insulin resistance in women with T2D (Fig 3).

**SNPs previously associated with GDM/T2D in India**

None of the 6 SNPs previously associated with either GDM or T2D in Indian populations was here associated with GDM defined using either WHO1999 or WHO2013 criteria. (Table 2, supplementary table 5).

**Previously reported GDM risk loci**

Out of the 12 selected previously studied GDM risk loci, the T allele of the missense SNP rs5219 in the *KCNJ11* gene was nominally associated with GDM1999 (p= 0.019)(table 3).

Contrary to previously reported results, the risk allele A of SNP rs11708067 in the *ADCY5* gene showed reduced risk in GDM2013 (p=0.037) (table 3) but not GDM1999 women.

The SNP rs2796441 in the*TLE1* gene was associated with decreased insulin secretion (p=0.013) (Supplementary Table 2).

**Previously reported T2D loci**

The risk allele C of SNP rs13389219 in the *GRB14* gene was associated with GDM1999 (p=0.022, table 4) but not with GDM2013 (p= 0.058, table 4).

The T2D risk allele T of SNP rs11920090 in the intron of the *SLC2A2* gene was associated with GDM2013 (p= 0.030) (table 4). The same SNP was also associated with GDM when defined as 2-hour glucose ≥ 8.5, (p=0.032), FBS ≥ 5.1 (p=0.053), FBS ≥ 5.1 AND 2-hour glucose ≥ 8.5 both (p=0.050) (Supplementary Table 5).

The T2D risk allele A of SNP rs11605924 in the *CRY2* gene was surprisingly associated with reduced risk of GDM1999 (p=0.025)(table 4). The same allele was

also associated with lower 2-hour glucose levels (p = 0.038) (supplementary table 4). The same SNP associated with GDM subjects defined using glucose "cut-off" level as 2-hour glucose ≥ 7.8 **(**p=0.024)(supplementary table 5) and glucose cut off threshold 2-hour glucose ≥ 8.5, **(**p=0.028) (supplementary table 5).

The risk allele A of SNP rs1552224 in the *CENTD2* locus was associated with decreased risk in GDM2013 women (p=0.001) (table 3). The same allele also associated with GDM defined with FBS cut-off of ≥ 5.1 (p=0.007) (Supplementary Table 5).

**Association with insulin secretion and insulin resistance**

12 SNPs previously associated with insulin secretion were here tested for association with HOMA2-B in pregnant Punjabi women. T2D risk allele A in rs11071657 at the *FAM148B* locus associated with increased insulin secretion (p=0.044) (table 5).

Among 6 SNPs previously associated with measures of insulin resistance, 3 SNPs here associated with HOMA2-IR. The C allele of rs7607980 in the *COBLL1* gene associated with decreased HOMA2-IR (p = 0,0001). The C allele of rs13389219 near *GRB14* (p = 0,026) and A allele of rs10423928 in the intron of the *GIPR* gene (p = 0.012) associated with increased HOMA2-IR (table 6).

**Association with GDM defined by various cut-off thresholds based on WHO1999 and WHO2013**

We next assessed the association of the selected SNPs with GDM as defined by WHO1999 and WHO2013 criteria to explore whether changing the criteria would influence the genetic associations GDM was defined by (i) FBS ≥ 5.1, (ii) FBS ≥ 7.0, (iii) 2-hour glucose ≥ 7.8, (iv) 2-hour glucose ≥ 8.5, (v) FBS ≥ 5.1 AND 2 hour glucose ≥ 8 and (vi) FBS ≥ 7.0 AND 2-hour glucose ≥ 7.8. GDM prevalence according to these criteria is shown in fig 4. SNP rs6467136 of *GCCI-PAX4* was associated with GDM defined using (i) FBS ≥ 7.0 (p=0.010), (ii) 2-hour glucose ≥ 8.5 (p=0.044), and (iii) FBS ≥ 7.0 AND 2-hour glucose ≥ 7.8 (p=0.005) (supplementary table 5).

A significant association was seen between SNPs rs7903146 in the *TCF7L2* gene (p=0.045), rs1799999 in *PPIR3A* (p=0.029), and rs11063069 in *CCND2* (p=0.046) with GDM defined using FBS ≥ 5.1 AND 2-hour glucose ≥ 8.5 (supplementary table 5).

rs10401969 of *SUGP1* (p=0.031)was associated with GDM criteria FBS ≥ 5.1 whereas SNP rs459193 of *ANKRD55* (p=0.045) associated with glucose "cut off" threshold as FBS ≥ 7.0. SNP rs6943153 in *GRB10* associated with 2-hour glucose ≥ 8.5 as cut-off value (p=0.040) (supplementary table 5).

Using "cut off" threshold as FBS ≥ 7.0 AND glucose ≥ 7.8, SNPs rs17168486 of *DGKB* (p=0.039), rs2191349 of *DGKB/TMEM195* (p=0.017), and rs689 of *INS, INS-IGF2*(p=0.038) showed associations with GDM (supplementary table 5).

## Discussion

In the present study, we investigated the genetic basis of gestational diabetes mellitus in Punjabi Indian women. Previously reported GDM and T2D loci in Indian as well as European populations were assessed for association with risk of GDM and related traits in 4018 pregnant women of Punjabi descent. This is the largest study investigating the genetic basis of GDM anywhere in the world [15, 16, 19, 27].

The genetic variants in the *HMG20A* and *HNF4A* genes which previously have been associated with risk of T2Dand GDM in South India [27] were not associate with GDM nor T2D in Punjabi women This could be due to differences in allele frequencies between the North and South Indian populations, which are ethnically quite distinctive populations [34]. The Punjabi Indian population belongs to the "Ancestral North Indians" group and shares genetic similarities with populations from Middle East, Central Asia and to some degree Europe whereas the South Indian population genetically belongs to the "Ancestral South Indian" group and is distinct from the Ancestral North Indian and East Asian populations [34]. The frequency differences of some genotypes clearly support these differences. The frequency of the risk allele G in the *HMG20A* SNP rs7178572 was 52.08% in the Punjabi Indian population whereas in the South Indian population, this was 46.1%. The

corresponding frequencies for the risk allele A in the *HNF4A* SNP rs4812829 were 28.97% and 35.15% respectively.

Interestingly, no associations were seen for any of the GDM or T2D loci selected from studies based on either Indian or European populations. The only GWAS on GDM till date was carried out in South Korea and reported an association with variants in the *CDKAL1* and *MTNR1B* loci. The CDK5 regulatory subunit associated protein 1 like 1 coding gene *CDKAL1* is highly expressed in pancreas, skeletal muscle and brain and specifically inhibits activity of the serine / threonine protein kinase cyclin-dependent kinase 5 (CDK5). CDK5 activation leads to inhibition of insulin secretion, particularly in a high glucose environment [35]. Inhibition of this activity could protect pancreatic beta cells from glucotoxicity [36]. The T2D risk variant in the melatonin receptor 1B coding *MTNR1B* gene modulates insulin release and melatonin treatment inhibited insulin secretion, with risk allele carriers exhibiting higher glucose levels. T2D risk locus in *MTNR1B* has been successfully replicated for association with GDM in Norway [16]. In the present study, we did not see an association between this variant and GDM in the Punjabi women.

T2D risk variants in the *CRY2* (WHO1999), *CENTD2* (WHO2013) and the *ADCY5* (WHO2013) genes were here protective for GDM. *CRY2* codes for the cryptochrome protein involved in the regulation of the circadian clock. Risk allele carriers of the rs11708067 SNP in *ADCY5* has been previously shown to reduce *ADCY5* expression in pancreatic beta cells. Moreover, *ADCY5* was shown to be indispensable for coupling glucose to insulin secretion in human islets [37].

Among 6 previous insulin resistance loci, 3 here showed an association with HOMA2-IR. The C allele in rs7607980 in the *COBLL1* gene previously associated with lower serum insulin and insulin resistance in overweight and obese children [38]. *COBLL1* codes for Cordon-Bleu WH2 Repeat Protein Like 1 protein.

rs13389219 near the growth factor receptor bound protein 14 coding *GRB14* and rs10423928 in the gastric inhibitory polypeptide receptor coding *GIPR* also here associated with HOMA2-IR. To our knowledge, this is the first report of insulin resistance loci during pregnancy in the North Indian population.

The most stringent interpretation of WHO2013 criteria resulted in the association of the most consistently replicated T2D risk SNP at the *TCF7L2* locus. Few other novel

associations included SNPs at *ANKRK55*, *GRB10* and 2 SNPs at the *DGKB* locus. This could be indicative that GDM in India is akin to IGT in Europe and perhaps stricter interpretations of current GDM criteria are closer to T2D.

Maternal diabetes significantly increases the risk of congenital malformations by 3-4 fold compared to pregnant women with NGT. While we in previous work have shown the key role of environmental factors for risk of GDM, not at least ethnicity and family history of T2D or GDM, we here wanted to explore more in detail the underlying genetic contributions.

Taken together, the results demonstrate that GDM in women from Punjab in Northern India shows a clear genetic component, which is mostly shared with GDM in other parts of the world. However, the direction of the effect can differ; some T2D risk variants were in fact protective for GDM in these Indian women.

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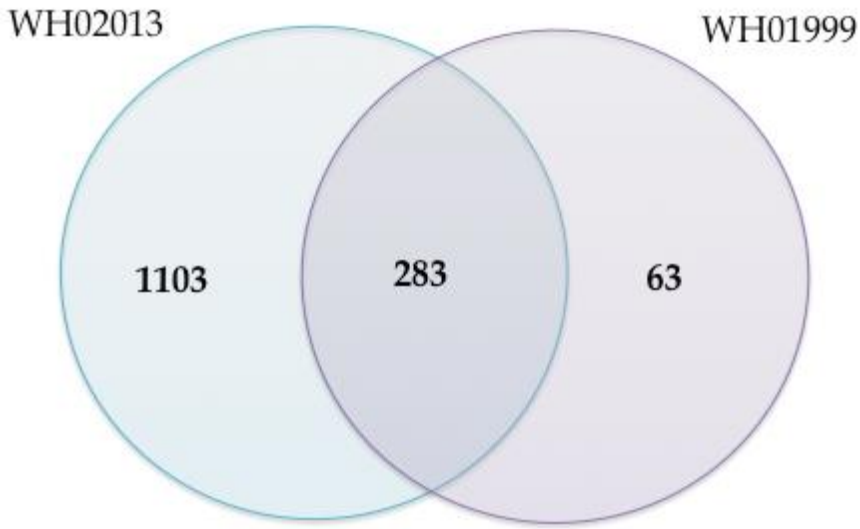


**Figure 1. Number of GDM women according to WHO2013 and WHO1999 criteria**

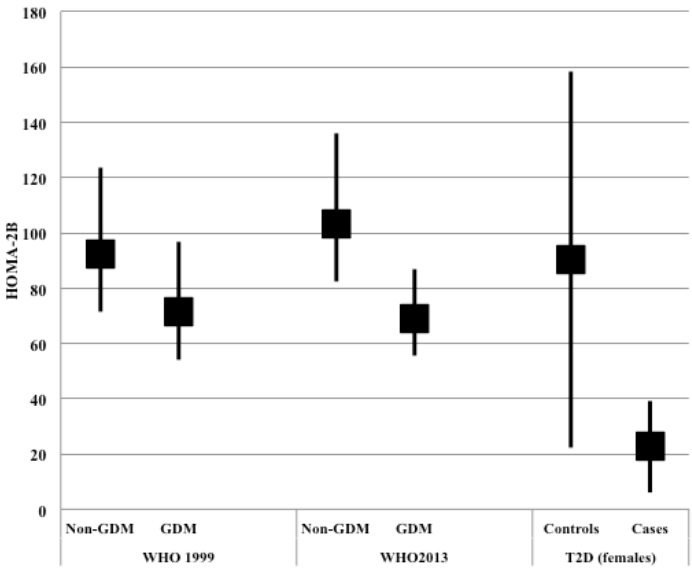


**Fig 2. Insulin secretion (HOMA-B) in GDM, T2D, normal glucose tolerant non pregnant women and healthy pregnant Punjabi women. T2D and data calculated from Been et al, Nutr Metab Cardiovasc Dis. 2013.**

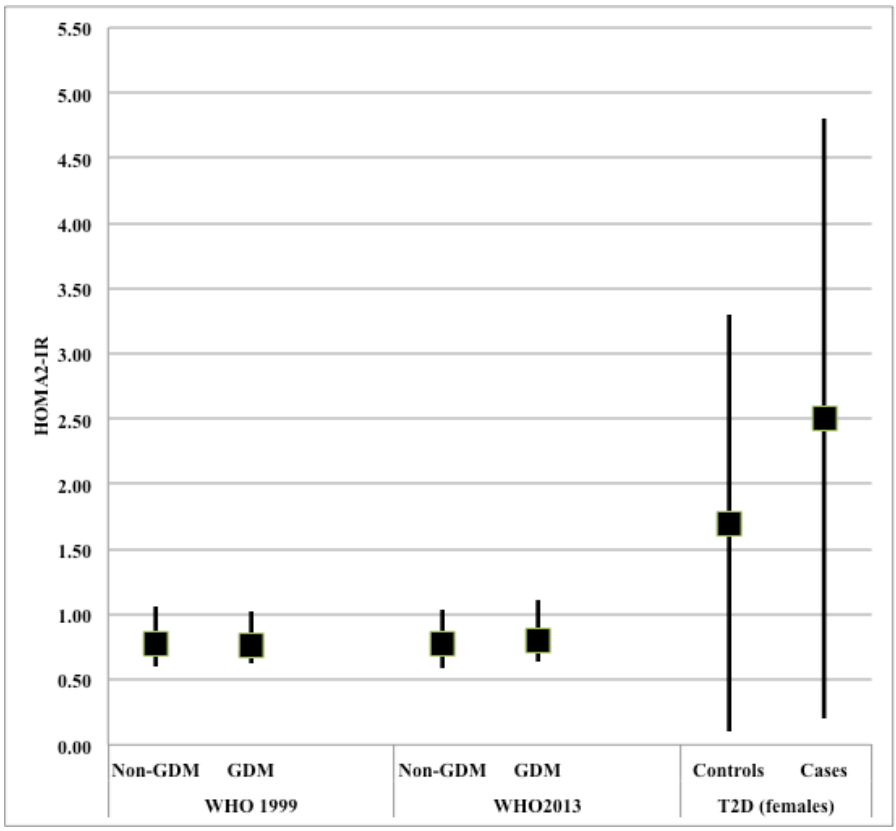


**Fig 3. Insulin resistance (HOMA-IR) in GDM, T2D, non-pregnant normal glucose tolerant and pregnant Punjabi women with NGT. T2D and data calculated from Been et al, Nutr Metab Cardiovasc Dis. 2013.**

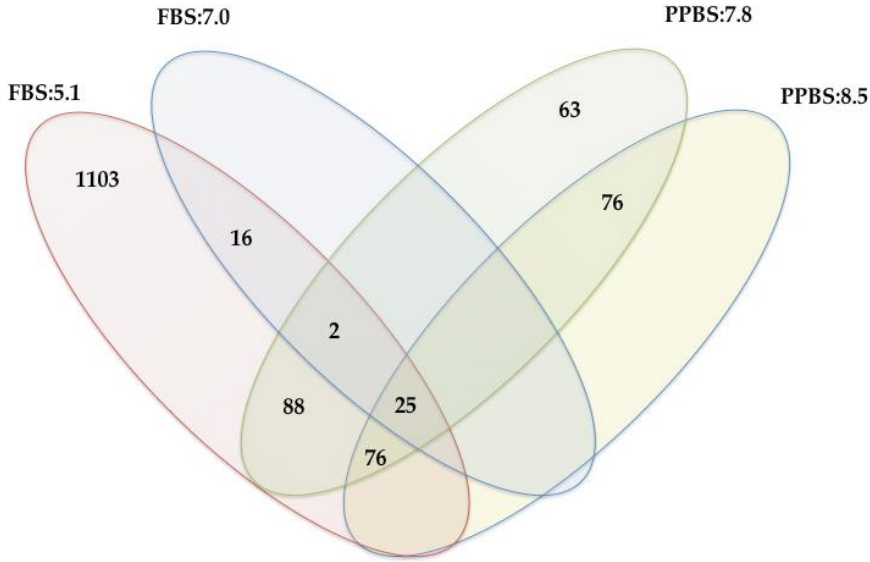


**Fig 4. Distribution of GDM according to WHO1999 and WHO2013 criteria. FBS = fasting blood sugar, PPBS = postprandial blood sugar.**

| Table 1. Study population characteristics | | | |
|---|---|---|---|
| | N | Mean | Stddev |
| Age (years) | 4018 | 21.41 | 3.40 |
| BMI | 4018 | 24.11 | 4.34 |
| Fasting plasma glucose (mmol/l) | 4018 | 4.812 | 0.76 |
| plasma insulin (pmol) | 4018 | 54.25 | 61.86 |
| 2 hour glucose (venous, mmol/l) | 4018 | 6.20 | 1.37 |
| homa2_b with acceptable steady state glucose and insulin values | 3680 | 104.02 | 55.71 |
| homa2_ir with acceptable steady state glucose and insulin values | 3680 | 0.97 | 0.74 |

**Table 2: Association of previously reported GDM and T2D loci from Indian population based studies with risk of GDM according to both criteria**

| genotype | EA | Chr | Gene/nearest gene | Location | OR_WHO 1999 | lower CI | upper CI | p_who 1999 | OR_WHO2013 | lower CI | upper CI | p_who 2013 | n |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs998451_A | A | 2 | TMEM163 | intron | 0,987 | 0,795 | 1,224 | 0,902 | 0,959 | 0,843 | 1,090 | 0,518 | 3882 |
| rs1799999_A | A | 7 | PPP1R3A | missense | 0,862 | 0,728 | 1,020 | 0,083 | 0,997 | 0,905 | 1,098 | 0,953 | 3890 |
| rs689_A | A | 11 | INS | 5'UTR | 1,077 | 0,879 | 1,319 | 0,474 | 1,033 | 0,914 | 1,167 | 0,603 | 3903 |
| rs9552911_A | | 13 | SGCG | intron | 1,057 | 0,830 | 1,347 | 0,653 | 1,017 | 0,875 | 1,183 | 0,824 | 3890 |
| rs4812829_A | A | 20 | HNF4A | intron | 1,040 | 0,871 | 1,240 | 0,667 | 0,988 | 0,890 | 1,096 | 0,814 | 3801 |
| rs7178572_G | G | 15 | HMG20A | intron | 0,988 | 0,832 | 1,173 | 0,891 | 1,017 | 0,921 | 1,122 | 0,743 | 3541 |

## Table 3: Association of previously reported GDM loci with risk of GDM according to both criteria

| | | | | | WHO 1999 | | | | WHO 2013 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | EA | Chr | Gene/nearest gene | Location | OR | CI(lower) | CI(upper) | p-value | OR | CI(lower) | CI(upper) | p-value | n |
| rs9939609_A | A | 16 | FTO | intron | 1,042 | 0,860 | 1,262 | 0,676 | 0,988 | 0,884 | 1,105 | 0,834 | 3120 |
| rs2796441_G | G | 9 | TLE 1 | intergenic | 0,993 | 0,843 | 1,169 | 0,929 | 1,072 | 0,975 | 1,179 | 0,152 | 3905 |
| rs560887_C | C | 2 | G6PC2/ABCB11 | intron | 1,182 | 0,920 | 1,520 | 0,191 | 1,114 | 0,967 | 1,284 | 0,134 | 3910 |
| rs11708067_A | A | 3 | ADCY5 | intron | 0,983 | 0,814 | 1,188 | 0,860 | 0,888 | 0,794 | 0,993 | **0,037** | 3877 |
| rs7754840_C | C | 6 | CDKAL 1 | intron | 0,878 | 0,727 | 1,061 | 0,179 | 0,966 | 0,869 | 1,073 | 0,518 | 3721 |
| rs1111875_C | C | 10 | HHEX | intergenic | 0,905 | 0,771 | 1,064 | 0,226 | 1,058 | 0,962 | 1,162 | 0,246 | 3901 |
| rs7756992_G | G | 6 | CDKAL 1 | intron | 0,913 | 0,757 | 1,101 | 0,340 | 0,975 | 0,876 | 1,085 | 0,645 | 3686 |
| rs10811661_T | T | 9 | CDKN2A/2B | intergenic | 0,990 | 0,776 | 1,263 | 0,936 | 1,088 | 0,947 | 1,251 | 0,233 | 3890 |
| rs4402960_T | T | 3 | IGF2BP2 | intron | 1,024 | 0,871 | 1,204 | 0,772 | 0,950 | 0,864 | 1,045 | 0,293 | 3750 |
| rs13266634_C | C | 8 | SLC30A8 | coding-missense | 0,969 | 0,798 | 1,177 | 0,751 | 0,972 | 0,872 | 1,084 | 0,614 | 3898 |
| rs10010131_G | G | 4 | WFS 1 | intron | 1,138 | 0,950 | 1,362 | 0,160 | 0,999 | 0,902 | 1,108 | 0,992 | 3843 |
| rs5219_T | T | 11 | KCNJ11 | coding-missense | 1,211 | 1,032 | 1,422 | **0,019** | 1,000 | 0,907 | 1,102 | 0,999 | 3595 |

## Table 4: Association of previously reported T2D loci with risk of GDM according to both criteria

| | | | | | WHO 1999 | | | | WHO 2013 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | EA | Chr | Gene/nearest gene | Location | OR | CI(lower) | CI(upper) | p-value | OR | CI(lower) | CI(upper) | p-value | n |
| rs2296172_G | G | 1 | MACF1 | coding-missense | 0,925 | 0,711 | 1,204 | 0,562 | 1,043 | 0,896 | 1,213 | 0,588 | 3847 |
| rs340874_C | C | 1 | PROX1 | intergenic | 0,948 | 0,804 | 1,117 | 0,521 | 0,966 | 0,878 | 1,062 | 0,476 | 3709 |
| rs7578597_T | T | 2 | THADA | coding-missense | 0,906 | 0,729 | 1,127 | 0,377 | 0,927 | 0,808 | 1,063 | 0,277 | 3710 |
| rs243088_T | T | 2 | BCL 11A | intergenic | 1,105 | 0,941 | 1,299 | 0,224 | 1,072 | 0,974 | 1,181 | 0,156 | 3717 |
| rs7593730_T | T | 2 | RBMS1/ITGB6 | intronic | 1,019 | 0,849 | 1,224 | 0,836 | 0,996 | 0,889 | 1,115 | 0,939 | 3906 |
| rs7607980_C | C | 2 | COBL1 | coding-missense | 0,958 | 0,736 | 1,247 | 0,751 | 0,951 | 0,815 | 1,110 | 0,523 | 3885 |
| rs13389219_C | C | 2 | GRB14 | intergenic | 1,256 | 1,033 | 1,528 | **0,022** | 1,110 | 0,996 | 1,236 | **0,058** | 3829 |
| rs7578326_A | A | 2 | KIAA1486/IRS1 | intron of uncharacterized LOC646736 | 0,974 | 0,800 | 1,184 | 0,789 | 0,985 | 0,878 | 1,105 | 0,795 | 3600 |
| rs2943641_C | C | 2 | IRS1 | intergenic | 0,927 | 0,767 | 1,120 | 0,432 | 0,977 | 0,874 | 1,092 | 0,679 | 3643 |
| rs4675095_A | A | 2 | IRS1 | intron | 1,113 | 0,871 | 1,422 | 0,391 | 1,040 | 0,905 | 1,196 | 0,580 | 3817 |
| rs831571_C | C | 3 | PSMD6 | intergenic | 1,029 | 0,845 | 1,252 | 0,777 | 0,935 | 0,833 | 1,051 | 0,261 | 3726 |
| rs4607103_C | C | 3 | ADAMTS9-AS2 | intron | 1,146 | 0,982 | 1,337 | **0,083** | 1,002 | 0,913 | 1,099 | 0,971 | 3884 |
| rs11920090_T | T | 3 | SLC2A2 | intron | 1,190 | 0,933 | 1,517 | 0,161 | 1,164 | 1,015 | 1,335 | **0,030** | 3606 |
| rs6815464_C | C | 4 | MAEA | intron | 1,042 | 0,833 | 1,305 | 0,716 | 1,032 | 0,903 | 1,180 | 0,640 | 3722 |
| rs459193_G | G | 5 | ANKRD55 | intergenic | 0,990 | 0,841 | 1,167 | 0,908 | 1,072 | 0,972 | 1,181 | 0,163 | 3884 |
| rs4457053_G | G | 5 | ZBED3 | intron of ZBED3-AS1 | 1,059 | 0,869 | 1,290 | 0,572 | 0,955 | 0,848 | 1,076 | 0,454 | 3579 |
| rs9470794_C | C | 6 | ZFAND3 | intron | 1,079 | 0,857 | 1,359 | 0,519 | 1,054 | 0,911 | 1,218 | 0,481 | 3608 |
| rs17168486_T | T | 7 | DGKB | intergenic | 0,991 | 0,835 | 1,178 | 0,921 | 0,975 | 0,881 | 1,078 | 0,622 | 3855 |
| rs2191349_T | T | 7 | DGKB/TMEM195 | intergenic | 1,042 | 0,885 | 1,229 | 0,620 | 1,003 | 0,911 | 1,103 | 0,956 | 3903 |
| rs864745_T | T | 7 | JAZF1 | intron | 0,986 | 0,835 | 1,165 | 0,870 | 1,022 | 0,922 | 1,132 | 0,681 | 3876 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs4607517_A | A | 7 | GCK | intergenic | 1,046 | 0,826 | 1,324 | 0,708 | 1,013 | 0,881 | 1,164 | 0,861 | 3903 |
| rs17133918_T | C | 7 | GRB10 | intron | 1,038 | 0,871 | 1,238 | 0,675 | 0,976 | 0,880 | 1,083 | 0,651 | 3907 |
| rs933360_A | A | 7 | GRB10 | intron | 1,033 | 0,873 | 1,224 | 0,703 | 1,032 | 0,934 | 1,140 | 0,541 | 3905 |
| rs6943153_T | C | 7 | GRB10 | intron | 0,869 | 0,732 | 1,032 | 0,110 | 0,954 | 0,862 | 1,057 | 0,369 | 3602 |
| rs6467136_G | G | 7 | GCC1-PAX4 | intergenic | 1,119 | 0,955 | 1,311 | 0,166 | 0,977 | 0,890 | 1,073 | 0,625 | 3593 |
| rs516946_C | C | 8 | ANK1 | intron | 1,011 | 0,828 | 1,235 | 0,916 | 1,095 | 0,973 | 1,232 | 0,131 | 3922 |
| rs896854_T | T | 8 | TP53INP1 | intron | 0,976 | 0,833 | 1,143 | 0,759 | 0,973 | 0,885 | 1,069 | 0,570 | 3903 |
| rs7034200_A | A | 9 | GLIS3 | intron | 0,985 | 0,839 | 1,155 | 0,849 | 1,031 | 0,939 | 1,132 | 0,525 | 3868 |
| rs13292136_C | C | 9 | TLE4 (CHCHD9) | intergenic | 0,946 | 0,757 | 1,183 | 0,628 | 0,982 | 0,861 | 1,121 | 0,793 | 3706 |
| rs12571751_A | A | 10 | ZMIZ1 | intron | 0,865 | 0,737 | 1,016 | **0,077** | 0,966 | 0,875 | 1,066 | 0,490 | 3601 |
| rs553668_A | A | 10 | ADRA2A | UTR-3 | 1,177 | 0,993 | 1,396 | **0,060** | 1,078 | 0,972 | 1,196 | 0,155 | 3666 |
| rs10885122_G | G | 10 | ADRA2A | intergenic | 1,034 | 0,841 | 1,271 | 0,754 | 1,050 | 0,932 | 1,182 | 0,426 | 3683 |
| rs163184_G | G | 11 | KCNQ1 | intron | 0,903 | 0,762 | 1,070 | 0,237 | 1,001 | 0,908 | 1,104 | 0,980 | 3713 |
| rs2237895_C | C | 11 | KCNQ1 | intron | 0,964 | 0,817 | 1,137 | 0,664 | 1,013 | 0,920 | 1,116 | 0,790 | 3682 |
| rs11605924_A | A | 11 | CRY2 | intron | 0,840 | 0,721 | 0,979 | **0,025** | 1,009 | 0,920 | 1,106 | 0,854 | 3909 |
| rs7944584_A | A | 11 | MADD | intron | 0,917 | 0,744 | 1,131 | 0,417 | 1,094 | 0,967 | 1,237 | 0,155 | 3553 |
| rs174550_T | T | 11 | FADS1 | intron | 0,947 | 0,763 | 1,175 | 0,621 | 0,964 | 0,851 | 1,092 | 0,568 | 3908 |
| rs1552224_A | A | 11 | CENTD2 | intergenic | 0,924 | 0,752 | 1,136 | 0,453 | 0,818 | 0,723 | 0,924 | **0,001** | 3911 |
| rs11063069_G | G | 12 | CCND2 | intergenic | 0,998 | 0,804 | 1,239 | 0,987 | 1,043 | 0,915 | 1,190 | 0,526 | 3671 |
| rs10842994_C | C | 12 | KLHDC5 | intergenic | 1,138 | 0,896 | 1,445 | 0,289 | 0,971 | 0,846 | 1,114 | 0,671 | 3906 |
| rs1153188_A | A | 12 | DCD | intergenic | 1,153 | 0,930 | 1,429 | 0,193 | 1,014 | 0,898 | 1,144 | 0,824 | 3912 |
| rs1531343_C | C | 12 | HMGA2 | intron of pseudogene | 0,836 | 0,678 | 1,031 | **0,094** | 0,905 | 0,801 | 1,021 | 0,105 | 3915 |
| rs7961581_C | C | 12 | TSPAN8,LGR5 | intergenic | 0,917 | 0,775 | 1,085 | 0,314 | 1,026 | 0,928 | 1,136 | 0,614 | 3703 |
| rs7957197_T | T | 12 | OASL/TCF1/HNF 1A | intron of QASL | 0,878 | 0,657 | 1,173 | 0,379 | 1,004 | 0,831 | 1,212 | 0,968 | 3924 |
| rs17271305_G | G | 15 | VPS13C | intron | 1,020 | 0,860 | 1,209 | 0,819 | 0,928 | 0,837 | 1,029 | 0,158 | 3825 |
| rs11071657_A | A | 15 | FAM148B | intergenic | 1,030 | 0,870 | 1,220 | 0,728 | 0,926 | 0,837 | 1,024 | 0,136 | 3897 |
| rs7177055_A | A | 15 | HMG20A | intergenic | 1,001 | 0,851 | 1,177 | 0,994 | 0,985 | 0,896 | 1,081 | 0,745 | 3907 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11634397_G | G | 15 | ZFAND6 | intergenic | 0,894 | 0,761 | 1,049 | 0,169 | 0,966 | 0,878 | 1,063 | 0,478 | 3910 |
| rs8042680_A | A | 15 | PRC1 | intron | 0,894 | 0,764 | 1,047 | 0,164 | 0,997 | 0,904 | 1,100 | 0,958 | 3887 |
| rs7202877_T | T | 16 | BCAR1 | intergenic | 1,214 | 0,895 | 1,646 | 0,213 | 1,047 | 0,877 | 1,250 | 0,613 | 3915 |
| rs8090011_G | G | 18 | LAMA1 | intron | 0,955 | 0,815 | 1,119 | 0,571 | 0,931 | 0,847 | 1,022 | 0,134 | 3911 |
| rs10401969_C | C | 19 | SUGP1 | intron | 0,963 | 0,728 | 1,274 | 0,791 | 0,860 | 0,729 | 1,015 | **0,074** | 3605 |
| rs8108269_G | G | 19 | GIPR | intergenic | 1,027 | 0,858 | 1,230 | 0,770 | 1,078 | 0,969 | 1,198 | 0,167 | 3508 |
| rs10423928_A | A | 19 | GIPR | intron | 0,858 | 0,679 | 1,085 | 0,201 | 1,060 | 0,932 | 1,207 | 0,374 | 3911 |
| rs6017317_G | G | 20 | FITM2-R3HDML-HNF4A | intergenic | 0,961 | 0,815 | 1,134 | 0,641 | 0,983 | 0,890 | 1,085 | 0,728 | 3758 |
| rs5945326_A | A | X | DUSP9 | intergenic | 0,957 | 0,816 | 1,121 | 0,583 | 1,016 | 0,921 | 1,122 | 0,745 | 3589 |

## Table 5 Association of selected loci with insulin secretion (HOMA2-B)

| SNP | EA | Chr | Gene/nearest gene | Location | Beta | SE | p-value | N |
|---|---|---|---|---|---|---|---|---|
| rs340874_C | C | 1 | PROX1 | intergenic | 0,009 | 0,011 | 0,388 | 3395 |
| rs560887_C | C | 2 | G6PC2/ABCB11 | intron | -0,004 | 0,016 | 0,818 | 3578 |
| rs11708067_A | A | 3 | ADCY5 | intron | 0,024 | 0,012 | 0,053 | 3556 |
| rs11920090_T | T | 3 | SLC2A2 | intron | -0,014 | 0,015 | 0,361 | 3301 |
| rs4607517_A | A | 7 | GCK | intergenic | 0,007 | 0,012 | 0,571 | 3372 |
| rs2191349_T | T | 7 | DGKB/TMEM195 | intergenic | -0,008 | 0,011 | 0,480 | 3575 |
| rs7034200_A | A | 9 | GLIS3 | intron | 0,002 | 0,016 | 0,922 | 3576 |
| rs10885122_G | G | 10 | ADRA2A | intergenic | -0,006 | 0,010 | 0,546 | 3545 |
| rs7944584_A | A | 11 | MADD | intron | -0,021 | 0,013 | 0,116 | 3372 |
| rs174550_T | T | 11 | FADS1 | intron | 0,011 | 0,014 | 0,435 | 3248 |
| rs7756992_G | G | 6 | CDKAL1 | intron | 0,011 | 0,014 | 0,446 | 3576 |
| rs11071657_A | A | 15 | FAM148B | intergenic | 0,023 | 0,011 | 0,044 | 3568 |



## Table 6: Association with HOMA-IR selected loci: insulin resistance SNPs

| SNP | EA | Chr | Gene/nearest gene | Location | Beta | SE | p-value | N |
|---|---|---|---|---|---|---|---|---|
| rs2943641_C | C | 2 | IRS1 | intergenic | -0,001 | 0,014 | 0,923 | 3337 |
| rs4675095_A | A | 2 | IRS1 | intron | -0,028 | 0,017 | 0,102 | 3500 |
| rs4607517_A | A | 7 | GCK | intergenic | 0,018 | 0,018 | 0,299 | 3576 |
| rs7607980_C | C | 2 | COBLL1 | coding-missense | -0,070 | 0,019 | 0,0001 | 3557 |
| rs13389219_C | C | 2 | GRB14 | intergenic | 0,029 | 0,013 | 0,026 | 3518 |
| rs10423928_A | A | 19 | GIPR | intron | 0,041 | 0,016 | 0,012 | 3585 |

**Supplementary table 1. T2D associated SNPs selected from previously published GWAS studies upto 2012 and GDM associated loci (*) from previous candidate and GWAS studies.**

| SNPs | GENE / nearest Gene | location | Chr | Locus | RA | OA | RAF | Trait | References |
|---|---|---|---|---|---|---|---|---|---|
| rs10923931 | *NOTCH2* | intron | 1 | 1p12 | T | G | 0.10 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs2296172 | *MACF1* | coding - missense | 1 | 1p34.3 | G | A | | T2D | A. Albrechtsen et al, Diabetologia, 2013 |
| rs340874 | *PROX1* | intergenic | 1 | 1q41 | C | T | 0.45 | Fasting glucose / insulin secretion / T2D | Dupuis et al Nat Genet 2010 |
| rs243021 | *BCL11A* | intergenic | 2 | 2p16.1 | A | G | 0.46 | T2D | Voight et al DIAGRAM 2010 |
| rs243088* | *BCL11A* | intergenic | 2 | 2p16.1 | T | A | 0.45 | T2D / GDM | Morris, naturegenetics 2012 |
| rs7578597 | *THADA* | coding - missense | 2 | 2p21 | T | C | 0.90 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs3923113 | *GRB14* | intergenic | 2 | 2q24.3 | A | C | 0.64 (0.74) | T2D | Kooner natgen 2012; Morris natgen, 2012 |
| rs13389219 | *GRB14* | intergenic | 2 | 2q24.3 | C | T | 0.60 | T2D | Morris, naturegenetics 2012 |
| rs7607980 | *COBL1* | coding - missense | 2 | 2q24.3 | C | T | | T2D | A. Albrechtsen et al, Diabetologia, 2013 |
| rs560887 | *G6PC2/ABCB11* | intron | 2 | 2q31.1 | C | T | 0.67 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs7578326 | *KIAA1486/IRS1* | intron of uncharacterized LOC646736 | 2 | 2q36.3 | A | G | 0.64 | T2D | Voight et al DIAGRAM2 2010 |
| rs2943641 | *IRS1* | intergenic | 2 | 2q36.3 | C | T | 0.63 | Fasting insulin /T2D / insulin sensitivity | Rung et al. Nat Genet 2010 |
| rs4675095 | *IRS1* | intron | 2 | 2q36.3 | A | T | 0.94 | fasting glucose/ insulin sensitivity | Dupuis et al Nat Genet 2010 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| rs7593730* | *RBMS1/ITGB6* | intronic | 2 | 9q24.2 | T | C | 0.23 | T2D / GDM | Qi et al. Hum Molec Gen. 2010 |
| rs4607103 | *ADAMTS9-AS2* | intron | 3 | 3p14.1 | C | T | 0.76 | T2D / GDM | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs831571 | *PSMD6* | intergenic | 3 | 3p14.1 | C | T | 1 (0.688) | Asian T2D | Cho natgen 2012 |
| rs1801282 | *PPARG* | coding - missense | 3 | 3p25.2 | C | G | 0.86 | T2D / Insulin sensitivity | DGI, MIT and LU, Science 2007 |
| rs11708067* | *ADCY5* | intron | 3 | 3q21.1 | A | G | 0.77 | T2D / 2hr glucose / Fasting Glucose / HOMA B / GDM | Saxena et al. Nat Genet 2010 |
| rs11920090 | *SLC2A2* | intron | 3 | 3q26.2 | T | A | 0.86 | Fasting glucose / HOMA B | Dupuis et al Nat Genet 2010 |
| rs4402960 | *IGF2BP2* | intron | 3 | 3q27.2 | T | G | 0.29 | T2D | DGI, MIT and LU, Science 2007 |
| rs10010131 | *WFS1* | intron | 4 | 4p16.1 | G | A | 0.60 | T2D | Sandhu et al nature genetics 2007, Lyssenko et al, NEJM 2008 |
| rs6815464 | *MAEA* | intron | 4 | 4p16.3 | C | G | 0.522 - 0.64 | Asian T2D | Cho natgen 2012 |
| rs459193 | *ANKRD55* | intergenic | 5 | 5q11.2 | G | A | 0.70 | T2D | Morris, naturegenetics 2012 |
| rs4457053 | *ZBED3* | intron of ZBED3-AS1 | 5 | 5q13.3 | G | A | 0.26 | T2D | Voight et al DIAGRAM2 2010 |
| rs9470794 | *ZFAND3* | intron | 6 | 6p21.2 | C | T | 0.50 (0.20) | Asian T2D | Cho natgen 2012 |
| rs7754840 | *CDKAL1* | intron | 6 | 6p22.3 | C | G | 0.30 | T2D | Steinthorsdottir, Nat Gen 2007, DGI, MIT and LU, Science 2007 |
| rs7756992 | *CDKAL1* | intron | 6 | 6p22.3 | G | A | 0.25 | T2D | Steinthorsdottir, Nat Gen 2007 |
| rs4607517 | *GCK* | intergenic | 7 | 7p13 | A | G | 0.20 | Fasting glucose/T2D / insulin sensitivity / HOMA B | Dupuis et al Nat Genet 2010 |
| rs864745 | *JAZF1* | intron | 7 | 7p15.1 | T | C | 0.50 | T2D | Zeggini, natgen, 2008, Lyssenko et al, |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | NEJM 2008 |
| rs2191349 | *DGKB/TMEM195* | intergenic | 7 | 7p21.2 | T | G | 0.50 | Fasting glucose / T2D / Insulin secretion | Dupuis et al Nat Genet 2010 |
| rs17168486 | *DGKB* | intergenic | 7 | 7p21.2 | T | C | 0.19 | T2D | Morris, naturegenetics 2012 |
| rs6467136 | *GCC1-PAX4* | intergenic | 7 | 7q32.1 | G | A | 0.50 (0.81) | Asian T2D | Cho natgen 2012 |
| rs516946 | *ANK1* | intron | 8 | 8p11.21 | C | T | 0.76 | T2D | Morris, naturegenetics 2012 |
| rs896854 | *TP53INP1* | intron | 8 | 8q22.1 | T | C | 0.48 | T2D | Voight et al DIAGRAM2 2010 |
| rs13266634 | *SLC30A8* | coding - missense | 8 | 8q24.11 | C | T | 0.70 | T2D | Sladek R Nature 2007 |
| rs10811661 | *CDKN2B* | intergenic | 9 | 9p21.3 | T | C | 0.80 | T2D | DGI, MIT and LU, Science 2007, Gupta, Diabetologia 2012, Wu Y, Diabetes 2008 |
| rs13292136 | *TLE4 (CHCHD9)* | intergenic | 9 | 9q21.31 | C | T | 0.93 | T2D | Voight et al DIAGRAM2 2010 |
| rs2796441 | *TLE1* | intergenic | 9 | 9q21.32 | G | A | 0.57 | T2D | Morris, naturegenetics 2012 |
| rs7034200 | *GLIS3* | intron | 9 | 9q24.2 | A | C | 0.50 | Fasting glucose /T2D/proinsulin to insulin / insulin secretion | Dupuis et al Nat Genet 2010 |
| rs12779790 | *CDC123,CAMK1 D* | intergenic | 10 | 10p13 | G | A | 0.18 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs12571751* | *ZMIZ1* | intron | 10 | 10q22.3 | A | G | 0.52 | T2D / GDM | Morris, naturegenetics 2012 |
| rs1111875* | *HHEX/IDE* | intergenic | 10 | 10q23.33 | C | T | 0.52 | T2D / GDM | DGI, MIT and LU, Science 2007 |
| rs7903146 | *TCF7L2* | intronic / promoter | 10 | 10q25.2 | T | C | 0.50 | T2D | Grant SFA, Nat genetics 2006, |
| rs553668 | *ADRA2A* | UTR-3 | 10 | 10q25.2 | A | G | 0.50 | T2D | Rosengren Science 2009 |
| rs10885122 | *ADRA2A* | intergenic | 10 | 10q25.2 | G | T | 0.90 | Fasting glucose / T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs7944584 | *MADD* | intron | 11 | 11p11.2 | A | T | 0.75 | Fasting proinsulin / | Dupuis et al Nat Genet 2010 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | T2D / Fasting glucose / HOMA B | |
| rs5219 | *KCNJ11* | coding - missense | 11 | 11p15.1 | T | C | 0.46 | T2D | DGI, MIT and LU, Science 2007 |
| rs2237895* | *KCNQ1* | intron | 11 | 11p15.4 | C | T | 0.33 | T2D / GDM | Yasuda natgen 2008 |
| rs163184 | *KCNQ1* | intron | 11 | 11p15.4 | G | T | 0.51 | T2D | Yasuda natgen 2008; Morris natgen, 2012 |
| rs2237892 | *KCNQ1* | intron | 11 | 11p15.4 | C | T | 0.69 | T2D | Yasuda Natgen 2008 |
| rs231362 | *KCNQ1* | intron | 11 | 11p15.5 | G | A | 0.52 | Fasting glucose / T2D | Voight et al DIAGRAM2 2010 |
| rs174550 | *FADS1* | intron | 11 | 11q12.2 | T | C | 0.63 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs1552224 | *CENTD2* | intergenic | 11 | 11q13.4 | A | C | 0.88 | T2D | Voight et al DIAGRAM2 2010 |
| rs10830963 | *MTNR1B* | intron | 11 | 11q14.3 | G | C | 0.30 | T2D / Fasting glucose / HOMA B | Prokopenko natgen 2008 |
| rs10842994 | *KLHDC5* | intergenic | 12 | 12p11.22 | C | T | 0.80 | T2D | Morris, naturegenetics 2012 |
| rs11063069 | *CCND2* | intergenic | 12 | 12p13.32 | G | A | 0.21 | T2D | Morris, naturegenetics 2012 |
| rs1153188 | *DCD* | intergenic | 12 | 12q13.2 | A | T | 0.73 | T2D | Zeggini et al Nat Gen 2009 |
| rs1531343 | *HMGA2* | intron of pseudogene | 12 | 12q14.3 | C | G | 0.10 | T2D | Voight et al DIAGRAM2 2010 |
| rs7961581 | *TSPAN8,LGR5* | intergenic | 12 | 12q21.1 | C | T | 0.27 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs35767 | *IGF1* | nearGene-5 | 12 | 12q23.2 | G | A | 0.88 | Fasting glucose/Fasting insulin/T2D / Insulin sensitivity | Dupuis et al Nat Genet 2010 |
| rs7957197 | *OASL/TCF1/HNF 1A* | intron of OASL | 12 | 12q24.31 | T | A | 0.85 | T2D | Voight et al DIAGRAM2 2010 |
| rs11071657 | *FAM148B* | intergenic | 15 | 15q22.2 | A | G | 0.77 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| rs17271305 | *VPS13C* | intron | 15 | 15q22.2 | G | A | 0.42 | 2hr glucose | Saxena et al. Nat Genet 2010 |
| rs7177055* | *HMG20A* | intergenic | 15 | 15q24.3 | A | G | 0.68 | T2D / GDM | Morris, naturegenetics 2012 |
| rs11634397 | *ZFAND6* | intergenic | 15 | 15q25.1 | G | A | 0.60 | T2D | Voight et al DIAGRAM2 2010 |
| rs8042680 | *PRC1* | intron | 15 | 15q26.1 | A | C | 0.22 | T2D | Voight et al DIAGRAM2 2010 |
| rs7202877 | *BCAR1* | intergenic | 16 | 16q23.1 | T | G | 0.89 | T2D | Morris, naturegenetics 2012 |
| rs8090011* | *LAMA1* | intron | 18 | 18p11.31 | G | C | 0.36 | T2D / GDM | Perry plos genetics 2012 |
| rs12970134 | *MC4R* | intergenic | 18 | 18q21.32 | A | G | 0.27 | T2D / BMI / waist circumference / insulin resistance | Chambers natgen 2008; Morris, naturegenetics 2012 |
| rs10401969 | *SUGP1* | intron | 19 | 19p13.3 | C | T | 0.08 | T2D | Morris, naturegenetics 2012 |
| rs10423928 | *GIPR* | intron | 19 | 19q13.32 | A | T | 0.17 | 2hr glucose / T2D | Saxena et al. Nat Genet 2010 |
| rs8108269 | *GIPR* | intergenic | 19 | 19q13.32 | G | T | 0.31 | T2D | Morris, naturegenetics 2012 |
| rs6017317 | *FITM2-R3HDML-HNF4A* | intergenic | 20 | 20q13.12 | G | T | 0.18 (0.54) | Asian T2D | Cho natgen 2012 |
| rs5945326* | *DUSP9* | intergenic | X | Xq28 | A | G | 0.79 | T2D / GDM | Voight et al DIAGRAM2 2010 |
| rs11605924* | *CRY2* | intron | 11 | 11p11.2 | A | C | 1.04 | T2D | Dupuis et al Nat Genet 2010 |
| rs9939609 | *FTO* | intron | 16 | 16q12.2 | A | T | 1.20 | T2D, obesity | Frayling et al Nat Genet 2007 |
| rs17133918 | *GRB10* | intron | 7 | 7p12.1 | C | T | | T2D | Prokopenko plos genetics 2013 |
| rs933360 | *GRB10* | intron | 7 | 7p12.1 | A | G | | T2D | Prokopenko plos genetics 2013 |
| rs6943153 | *GRB10* | intron | 7 | 7p12.1 | C | T | 0.0154 (beta) | fasting glucose /fasting insulin | Prokopenko plos genetics 2013 |
| rs7178572* | *HMG20A* | Intergenic | 15 | 7p12.1 | G | A | 1.09 | T2D / GDM | Perry plos genetics 2012; Kooner natgen 2012 |

**Supplementary Table 2a:Association of previously reported GDM loci with glycemic traits**

| depvar | genotype | beta | se | lower | upper | p | n | Gene Locus |
|---|---|---|---|---|---|---|---|---|
| LN_FBS_mmol | rs9939609_A | 0.000 | 0.004 | -0.008 | 0.008 | 0.939 | 3118 | *FTO* |
| LN_PPBS_mmol_ven | rs9939609_A | 0.000 | 0.005 | -0.011 | 0.010 | 0.926 | 3120 | |
| LN_PINS_pmol | rs9939609_A | -0.017 | 0.016 | -0.049 | 0.015 | 0.290 | 3120 | |
| LN_homa2_b_ss | rs9939609_A | -0.005 | 0.012 | -0.029 | 0.019 | 0.688 | 2856 | |
| LN_homa2_ir_ss | rs9939609_A | -0.018 | 0.013 | -0.044 | 0.009 | 0.186 | 2856 | |
| | | | | | | | | |
| LN_FBS_mmol | rs2796441_G | 0.004 | 0.004 | -0.003 | 0.011 | 0.270 | 3903 | *TLE1* |
| LN_PPBS_mmol_ven | rs2796441_G | -0.001 | 0.005 | -0.010 | 0.008 | 0.799 | 3905 | |
| LN_PINS_pmol | rs2796441_G | -0.016 | 0.014 | -0.043 | 0.012 | 0.268 | 3905 | |
| LN_homa2_b_ss | rs2796441_G | -0.026 | 0.011 | -0.047 | -0.005 | 0.014 | 3577 | |
| LN_homa2_ir_ss | rs2796441_G | -0.023 | 0.012 | -0.046 | 0.000 | 0.050 | 3577 | |
| | | | | | | | | |
| LN_FBS_mmol | rs560887_C | 0.006 | 0.005 | -0.005 | 0.016 | 0.283 | 3908 | *G6PC2/ABCB11* |
| LN_PPBS_mmol_ven | rs560887_C | 0.003 | 0.007 | -0.010 | 0.016 | 0.647 | 3910 | |
| LN_PINS_pmol | rs560887_C | -0.008 | 0.021 | -0.049 | 0.033 | 0.708 | 3910 | |
| LN_homa2_b_ss | rs560887_C | -0.004 | 0.016 | -0.034 | 0.027 | 0.818 | 3578 | |
| LN_homa2_ir_ss | rs560887_C | 0.017 | 0.017 | -0.017 | 0.051 | 0.323 | 3578 | |
| | | | | | | | | |
| LN_FBS_mmol | rs11708067_A | -0.008 | 0.004 | -0.016 | 0.000 | 0.055 | 3875 | *ADCY5* |
| LN_PPBS_mmol_ven | rs11708067_A | -0.006 | 0.005 | -0.017 | 0.004 | 0.252 | 3877 | |
| LN_PINS_pmol | rs11708067_A | 0.013 | 0.017 | -0.020 | 0.045 | 0.437 | 3877 | |
| LN_homa2_b_ss | rs11708067_A | 0.024 | 0.012 | 0.000 | 0.049 | 0.053 | 3556 | |
| LN_homa2_ir_ss | rs11708067_A | 0.010 | 0.014 | -0.017 | 0.037 | 0.466 | 3556 | |
| | | | | | | | | |
| LN_FBS_mmol | rs7754840_C | -0.001 | 0.004 | -0.008 | 0.007 | 0.847 | 3719 | *CDKAL1* |
| LN_PPBS_mmol_ven | rs7754840_C | -0.003 | 0.005 | -0.013 | 0.007 | 0.506 | 3721 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LN_PINS_pmol | rs7754840_C | 0.022 | 0.016 | -0.009 | 0.053 | 0.164 | 3721 | |
| LN_homa2_b_ss | rs7754840_C | 0.012 | 0.012 | -0.011 | 0.036 | 0.295 | 3402 | |
| LN_homa2_ir_ss | rs7754840_C | 0.015 | 0.013 | -0.011 | 0.041 | 0.260 | 3402 | |
| | | | | | | | | |
| LN_FBS_mmol | rs1111875_C | 0.004 | 0.004 | -0.002 | 0.011 | 0.210 | 3899 | *HHEX* |
| LN_PPBS_mmol_ven | rs1111875_C | 0.005 | 0.005 | -0.004 | 0.014 | 0.258 | 3901 | |
| LN_PINS_pmol | rs1111875_C | -0.008 | 0.014 | -0.035 | 0.019 | 0.567 | 3901 | |
| LN_homa2_b_ss | rs1111875_C | -0.011 | 0.011 | -0.032 | 0.009 | 0.283 | 3572 | |
| LN_homa2_ir_ss | rs1111875_C | -0.005 | 0.012 | -0.028 | 0.018 | 0.688 | 3572 | |
| | | | | | | | | |
| LN_FBS_mmol | rs7756992_G | -0.002 | 0.004 | -0.010 | 0.006 | 0.609 | 3684 | *CDKAL1* |
| LN_PPBS_mmol_ven | rs7756992_G | -0.002 | 0.005 | -0.012 | 0.008 | 0.754 | 3686 | |
| LN_PINS_pmol | rs7756992_G | 0.004 | 0.016 | -0.027 | 0.036 | 0.778 | 3686 | |
| LN_homa2_b_ss | rs7756992_G | 0.007 | 0.012 | -0.017 | 0.030 | 0.571 | 3372 | |
| LN_homa2_ir_ss | rs7756992_G | 0.000 | 0.013 | -0.026 | 0.026 | 0.990 | 3372 | |
| | | | | | | | | |
| LN_FBS_mmol | rs10811661_T | 0.002 | 0.005 | -0.008 | 0.012 | 0.757 | 3888 | *CDKN2A/2B* |
| LN_PPBS_mmol_ven | rs10811661_T | -0.003 | 0.007 | -0.016 | 0.010 | 0.661 | 3890 | |
| LN_PINS_pmol | rs10811661_T | -0.008 | 0.020 | -0.048 | 0.032 | 0.697 | 3890 | |
| LN_homa2_b_ss | rs10811661_T | 0.003 | 0.015 | -0.027 | 0.034 | 0.825 | 3561 | |
| LN_homa2_ir_ss | rs10811661_T | -0.003 | 0.017 | -0.037 | 0.030 | 0.856 | 3561 | |
| | | | | | | | | |
| LN_FBS_mmol | rs4402960_T | -0.004 | 0.003 | -0.010 | 0.003 | 0.311 | 3748 | *IGF2BP2* |
| LN_PPBS_mmol_ven | rs4402960_T | 0.007 | 0.005 | -0.002 | 0.016 | 0.116 | 3750 | |
| LN_PINS_pmol | rs4402960_T | -0.007 | 0.014 | -0.034 | 0.021 | 0.636 | 3750 | |
| LN_homa2_b_ss | rs4402960_T | 0.003 | 0.011 | -0.018 | 0.024 | 0.778 | 3439 | |
| LN_homa2_ir_ss | rs4402960_T | -0.012 | 0.012 | -0.035 | 0.011 | 0.304 | 3439 | |
| | | | | | | | | |
| LN_FBS_mmol | rs13266634_C | -0.004 | 0.004 | -0.012 | 0.004 | 0.360 | 3896 | *SLC30A8* |
| LN_PPBS_mmol_ven | rs13266634_C | -0.001 | 0.005 | -0.012 | 0.009 | 0.814 | 3898 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| LN_PINS_pmol | rs13266634_C | -0.014 | 0.016 | -0.046 | 0.017 | 0.371 | 3898 | |
| LN_homa2_b_ss | rs13266634_C | -0.005 | 0.012 | -0.029 | 0.019 | 0.692 | 3571 | |
| LN_homa2_ir_ss | rs13266634_C | -0.012 | 0.014 | -0.038 | 0.015 | 0.386 | 3571 | |
| | | | | | | | | |
| LN_FBS_mmol | rs10010131_G | 0.002 | 0.004 | -0.006 | 0.009 | 0.631 | 3841 | *WFS1* |
| LN_PPBS_mmol_ven | rs10010131_G | 0.006 | 0.005 | -0.004 | 0.016 | 0.234 | 3843 | |
| LN_PINS_pmol | rs10010131_G | -0.001 | 0.015 | -0.031 | 0.029 | 0.937 | 3843 | |
| LN_homa2_b_ss | rs10010131_G | -0.004 | 0.011 | -0.027 | 0.018 | 0.718 | 3521 | |
| LN_homa2_ir_ss | rs10010131_G | 0.002 | 0.013 | -0.023 | 0.027 | 0.877 | 3521 | |
| | | | | | | | | |
| LN_FBS_mmol | rs5219_T | -0.002 | 0.004 | -0.009 | 0.005 | 0.639 | 3593 | *KCNJ11* |
| LN_PPBS_mmol_ven | rs5219_T | 0.008 | 0.005 | -0.001 | 0.018 | 0.075 | 3595 | |
| LN_PINS_pmol | rs5219_T | 0.011 | 0.014 | -0.017 | 0.039 | 0.446 | 3595 | |
| LN_homa2_b_ss | rs5219_T | 0.007 | 0.011 | -0.014 | 0.028 | 0.534 | 3306 | |
| LN_homa2_ir_ss | rs5219_T | 0.001 | 0.012 | -0.023 | 0.024 | 0.940 | 3306 | |

**Supplementary table 3. Association of previously reported GDM loci with risk of GDM in Punjabi women based on different glucose cut-offs**

| Previously reported GDM loci risk allales | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| criteria | SNP | Chr | locus | location | effect allele | coeff | se | pval | n | n_cases |
| FBS 5.1 | rs9939609 | 16 | *FTO* | intron | A | 0.001 | 0.058 | 0.985 | 3120 | 982 |
| FBS 7.0 | rs9939609 | 16 | *FTO* | intron | A | 0.179 | 0.266 | 0.502 | 3120 | 30 |
| 2 hr 7.8 | rs9939609 | 16 | *FTO* | intron | A | 0.027 | 0.104 | 0.794 | 3120 | 219 |
| 2 hr 8.5 | rs9939609 | 16 | *FTO* | intron | A | -0.173 | 0.140 | 0.218 | 3120 | 127 |
| FBS 5.1 and PPBS 8.5 | rs9939609 | 16 | *FTO* | intron | A | -0.179 | 0.191 | 0.349 | 3120 | 68 |
| FBS 7.0 and PPBS 7.8 | rs9939609 | 16 | *FTO* | intron | A | 0.113 | 0.322 | 0.726 | 3120 | 21 |

| criteria | genotype | | *locus* | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs2796441 | 9 | *TLE 1* | intergenic | G | 0.070 | 0.049 | 0.153 | 3905 | 1264 |
| FBS 7.0 | rs2796441 | 9 | *TLE 1* | intergenic | G | -0.001 | 0.219 | 0.997 | 3905 | 43 |
| 2 hr 7.8 | rs2796441 | 9 | *TLE 1* | intergenic | G | -0.006 | 0.083 | 0.945 | 3905 | 320 |
| 2 hr 8.5 | rs2796441 | 9 | *TLE 1* | intergenic | G | -0.002 | 0.112 | 0.987 | 3905 | 172 |
| FBS 5.1 and PPBS 8.5 | rs2796441 | 9 | *TLE 1* | intergenic | G | -0.017 | 0.147 | 0.908 | 3905 | 97 |
| FBS 7.0 and PPBS 7.8 | rs2796441 | 9 | *TLE 1* | intergenic | G | 0.023 | 0.276 | 0.933 | 3905 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | 0.110 | 0.074 | 0.134 | 3910 | 1273 |
| FBS 7.0 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | 0.809 | 0.457 | 0.077 | 3910 | 43 |
| 2 hr 7.8 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | 0.126 | 0.129 | 0.329 | 3910 | 322 |
| 2 hr 8.5 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | - | 0.161 | 0.639 | 3910 | 172 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 0.076 | | | | |
| FBS 5.1 and PPBS 8.5 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | -0.139 | 0.207 | 0.503 | 3910 | 97 |
| FBS 7.0 and PPBS 7.8 | rs560887 | 2 | *G6PC2/ABCB11* | intron | C | 0.563 | 0.511 | 0.271 | 3910 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs11708067 | 3 | *ADCY5* | intron | A | -0.102 | 0.058 | 0.077 | 3877 | 1266 |
| FBS 7.0 | rs11708067 | 3 | *ADCY5* | intron | A | -0.068 | 0.257 | 0.792 | 3877 | 42 |
| 2 hr 7.8 | rs11708067 | 3 | *ADCY5* | intron | A | -0.049 | 0.097 | 0.618 | 3877 | 320 |
| 2 hr 8.5 | rs11708067 | 3 | *ADCY5* | intron | A | -0.111 | 0.129 | 0.390 | 3877 | 171 |
| FBS 5.1 and PPBS 8.5 | rs11708067 | 3 | *ADCY5* | intron | A | -0.005 | 0.175 | 0.978 | 3877 | 95 |
| FBS 7.0 and PPBS 7.8 | rs11708067 | 3 | *ADCY5* | intron | A | -0.413 | 0.301 | 0.169 | 3877 | 26 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.044 | 0.055 | 0.426 | 3721 | 1214 |
| FBS 7.0 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.531 | 0.285 | **0.062** | 3721 | 41 |
| 2 hr 7.8 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.106 | 0.095 | 0.267 | 3721 | 307 |
| 2 hr 8.5 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.066 | 0.127 | 0.602 | 3721 | 163 |
| FBS 5.1 and PPBS 8.5 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.194 | 0.173 | 0.263 | 3721 | 92 |
| FBS 7.0 and PPBS 7.8 | rs7754840 | 6 | *CDKAL 1* | intron | C | -0.469 | 0.350 | 0.181 | 3721 | 26 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs1111875 | 10 | *HHEX* | intergenic | C | 0.043 | 0.049 | 0.377 | 3901 | 1265 |
| FBS 7.0 | rs1111875 | 10 | *HHEX* | intergenic | C | -0.185 | 0.223 | 0.406 | 3901 | 43 |
| 2 hr 7.8 | rs1111875 | 10 | *HHEX* | intergenic | C | -0.082 | 0.084 | 0.331 | 3901 | 316 |
| 2 hr 8.5 | rs1111875 | 10 | *HHEX* | intergenic | C | 0.071 | 0.112 | 0.525 | 3901 | 170 |
| FBS 5.1 and PPBS 8.5 | rs1111875 | 10 | *HHEX* | intergenic | C | -0.007 | 0.147 | 0.962 | 3901 | 97 |
| FBS 7.0 and PPBS 7.8 | rs1111875 | 10 | *HHEX* | intergenic | C | -0.055 | 0.278 | 0.843 | 3901 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.042 | 0.056 | 0.450 | 3686 | 1205 |
| FBS 7.0 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.342 | 0.271 | 0.207 | 3686 | 41 |
| 2 hr 7.8 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.067 | 0.095 | 0.484 | 3686 | 305 |
| 2 hr 8.5 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.055 | 0.128 | 0.665 | 3686 | 163 |
| FBS 5.1 and PPBS 8.5 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.254 | 0.177 | 0.152 | 3686 | 92 |
| FBS 7.0 and PPBS 7.8 | rs7756992_G | 6 | *CDKAL 1* | intron | G | -0.202 | 0.327 | 0.537 | 3686 | 26 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.080 | 0.072 | 0.271 | 3890 | 1259 |
| FBS 7.0 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.240 | 0.351 | 0.494 | 3890 | 43 |
| 2 hr 7.8 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | -0.027 | 0.121 | 0.821 | 3890 | 316 |
| 2 hr 8.5 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.088 | 0.168 | 0.603 | 3890 | 170 |
| FBS 5.1 and PPBS 8.5 | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.079 | 0.222 | 0.724 | 3890 | 95 |
| FBS 7.0 and PPBS | rs10811661 | 9 | *CDKN2A/2B* | intergenic | T | 0.169 | 0.430 | 0.694 | 3890 | 27 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 7.8 | | | | | | | | | | |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs4402960 | 3 | *IGF2BP2* | intron | T | -0.062 | 0.049 | 0.208 | 3750 | 1210 |
| FBS 7.0 | rs4402960 | 3 | *IGF2BP2* | intron | T | -0.324 | 0.224 | 0.149 | 3750 | 43 |
| 2 hr 7.8 | rs4402960 | 3 | *IGF2BP2* | intron | T | 0.048 | 0.083 | 0.563 | 3750 | 307 |
| 2 hr 8.5 | rs4402960 | 3 | *IGF2BP2* | intron | T | 0.004 | 0.111 | 0.968 | 3750 | 168 |
| FBS 5.1 and PPBS 8.5 | rs4402960 | 3 | *IGF2BP2* | intron | T | -0.077 | 0.148 | 0.605 | 3750 | 93 |
| FBS 7.0 and PPBS 7.8 | rs4402960 | 3 | *IGF2BP2* | intron | T | -0.257 | 0.280 | 0.358 | 3750 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.023 | 0.056 | 0.678 | 3898 | 1263 |
| FBS 7.0 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.091 | 0.246 | 0.713 | 3898 | 43 |
| 2 hr 7.8 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.047 | 0.095 | 0.623 | 3898 | 319 |
| 2 hr 8.5 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.020 | 0.128 | 0.873 | 3898 | 171 |
| FBS 5.1 and PPBS 8.5 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | 0.013 | 0.171 | 0.937 | 3898 | 96 |
| FBS 7.0 and PPBS 7.8 | rs13266634 | 8 | *SLC30A8* | coding-missense | C | -0.275 | 0.296 | 0.353 | 3898 | 27 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs10010131 | 4 | *WFS 1* | intron | G | 0.005 | 0.053 | 0.928 | 3843 | 1257 |
| FBS 7.0 | rs10010131 | 4 | *WFS 1* | intron | G | 0.352 | 0.262 | 0.180 | 3843 | 41 |
| 2 hr 7.8 | rs10010131 | 4 | *WFS 1* | intron | G | 0.113 | 0.093 | 0.222 | 3843 | 315 |
| 2 hr 8.5 | rs10010131 | 4 | *WFS 1* | intron | G | 0.104 | 0.124 | 0.402 | 3843 | 168 |
| FBS 5.1 and PPBS | rs10010131 | 4 | *WFS 1* | intron | G | 0.239 | 0.170 | 0.160 | 3843 | 93 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 8.5 | | | | | | | | | | |
| FBS 7.0 and PPBS 7.8 | rs10010131 | 4 | *WFS 1* | intron | G | 0.311 | 0.331 | 0.347 | 3843 | 25 |

| criteria | genotype | | locus | | | coeff | se | pval | n | n_cases |
|---|---|---|---|---|---|---|---|---|---|---|
| FBS 5.1 | rs5219 | 11 | *KCNJ11* | coding-missense | T | -0.010 | 0.051 | 0.848 | 3595 | 1179 |
| FBS 7.0 | rs5219 | 11 | *KCNJ11* | coding-missense | T | 0.242 | 0.221 | 0.272 | 3595 | 40 |
| 2 hr 7.8 | rs5219 | 11 | *KCNJ11* | coding-missense | T | 0.162 | 0.084 | **0.055** | 3595 | 301 |
| 2 hr 8.5 | rs5219 | 11 | *KCNJ11* | coding-missense | T | 0.109 | 0.114 | 0.335 | 3595 | 160 |
| FBS 5.1 and PPBS 8.5 | rs5219 | 11 | *KCNJ11* | coding-missense | T | 0.105 | 0.151 | 0.486 | 3595 | 89 |
| FBS 7.0 and PPBS 7.8 | rs5219 | 11 | *KCNJ11* | coding-missense | T | -0.039 | 0.286 | 0.892 | 3595 | 25 |

**Supplementary table 4. Association of GDM loci with glycemic traitss**

| depvar | genotype | beta | se | lower | upper | p | n |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| LN_FBS_mmol | rs13389219_C | 0.002 | 0.004 | -0.005 | 0.010 | 0.575 | 3827 |
| LN_PPBS_mmol_ven | rs13389219_C | 0.009 | 0.005 | -0.001 | 0.019 | 0.074 | 3829 |
| LN_PINS_pmol | rs13389219_C | 0.026 | 0.016 | -0.004 | 0.057 | 0.091 | 3829 |
| LN_homa2_b_ss | rs13389219_C | 0.014 | 0.012 | -0.009 | 0.037 | 0.235 | 3518 |
| LN_homa2_ir_ss | rs13389219_C | 0.029 | 0.013 | 0.004 | 0.055 | 0.026 | 3518 |
| | | | | | | | |
| LN_FBS_mmol | rs11920090_T | 0.005 | 0.005 | -0.005 | 0.015 | 0.320 | 3605 |
| LN_PPBS_mmol_ven | rs11920090_T | 0.010 | 0.006 | -0.002 | 0.023 | 0.106 | 3606 |
| LN_PINS_pmol | rs11920090_T | 0.021 | 0.020 | -0.019 | 0.060 | 0.304 | 3606 |
| LN_homa2_b_ss | rs11920090_T | -0.014 | 0.015 | -0.043 | 0.016 | 0.361 | 3301 |
| LN_homa2_ir_ss | rs11920090_T | 0.002 | 0.017 | -0.031 | 0.035 | 0.916 | 3301 |
| | | | | | | | |
| LN_FBS_mmol | rs11605924_A | 0.003 | 0.003 | -0.003 | 0.010 | 0.316 | 3907 |
| LN_PPBS_mmol_ven | rs11605924_A | -0.009 | 0.004 | -0.018 | 0.000 | 0.039 | 3909 |
| LN_PINS_pmol | rs11605924_A | -0.015 | 0.014 | -0.042 | 0.011 | 0.262 | 3909 |
| LN_homa2_b_ss | rs11605924_A | -0.011 | 0.010 | -0.032 | 0.009 | 0.264 | 3583 |
| LN_homa2_ir_ss | rs11605924_A | -0.013 | 0.011 | -0.035 | 0.009 | 0.247 | 3583 |
| | | | | | | | |
| LN_FBS_mmol | rs1552224_A | -0.005 | 0.005 | -0.014 | 0.005 | 0.328 | 3909 |
| LN_PPBS_mmol_ven | rs1552224_A | 0.004 | 0.006 | -0.008 | 0.016 | 0.482 | 3911 |
| LN_PINS_pmol | rs1552224_A | -0.016 | 0.019 | -0.052 | 0.020 | 0.383 | 3911 |
| LN_homa2_b_ss | rs1552224_A | 0.003 | 0.014 | -0.024 | 0.031 | 0.817 | 3579 |
| LN_homa2_ir_ss | rs1552224_A | -0.017 | 0.016 | -0.047 | 0.014 | 0.282 | 3579 |

**Supplementary table 5. Association of selected T2D risk loci with risk of GDM in Punjabi women based on different glucose cut-offs**

| | | | | FBS = 5,1 | | | | | | FBS = 7,0 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | effect allele | Chr | Locus | n | n_cases | OR | CI(lower) | CI(upper) | pval | n | n_cases | OR | CI(lower) | CI(upper) | pval |
| rs2296172 | G | 1 | *MACF1* | 3847 | 1242 | 1.049 | 0.901 | 1.221 | 0.539 | 3847 | 42 | 0.803 | 0.383 | 1.680 | 0.559 |
| rs340874 | C | 1 | *PROX1* | 3709 | 1212 | 0.970 | 0.881 | 1.068 | 0.534 | 3709 | 40 | 1.059 | 0.684 | 1.640 | 0.797 |
| rs7578597 | T | 2 | *THADA* | 3710 | 1208 | 0.939 | 0.817 | 1.079 | 0.374 | 3710 | 40 | 0.929 | 0.500 | 1.723 | 0.814 |
| rs243088 | T | 2 | *BCL 11A* | 3717 | 1218 | 1.036 | 0.940 | 1.143 | 0.474 | 3717 | 41 | 1.088 | 0.702 | 1.688 | 0.706 |
| rs998451* | A | 2 | *TMEM163* | 3882 | 1268 | 0.949 | 0.833 | 1.081 | 0.431 | 3882 | 42 | 0.848 | 0.455 | 1.583 | 0.606 |
| rs7593730 | T | 2 | *RBMS1/ITGB6* | 3906 | 1268 | 1.012 | 0.901 | 1.135 | 0.846 | 3906 | 42 | 1.212 | 0.737 | 1.994 | 0.449 |
| rs7607980 | C | 2 | *COBL1* | 3885 | 1256 | 0.936 | 0.801 | 1.094 | 0.404 | 3885 | 43 | 0.701 | 0.319 | 1.540 | 0.376 |
| rs13389219 | C | 2 | *GRB14* | 3829 | 1246 | 1.083 | 0.972 | 1.207 | 0.148 | 3829 | 40 | 1.005 | 0.612 | 1.652 | 0.983 |
| rs560887 | C | 2 | *G6PC2/ABCB11* | 3910 | 1273 | 1.117 | 0.966 | 1.291 | 0.134 | 3910 | 43 | 2.246 | 0.917 | 5.501 | 0.077 |
| rs7578326 | A | 2 | *KIAA1486/IRS1* | 3600 | 1170 | 0.966 | 0.859 | 1.085 | 0.556 | 3600 | 40 | 0.961 | 0.574 | 1.610 | 0.881 |
| rs2943641 | C | 2 | *IRS1* | 3643 | 1191 | 0.972 | 0.868 | 1.087 | 0.616 | 3643 | 39 | 0.866 | 0.528 | 1.419 | 0.568 |
| rs4675095 | A | 2 | *IRS1* | 3817 | 1250 | 1.017 | 0.883 | 1.172 | 0.814 | 3817 | 40 | 0.869 | 0.469 | 1.609 | 0.655 |
| rs1801282 | C | 3 | *PPARG* | 3652 | 1196 | 0.999 | 0.864 | 1.155 | 0.993 | 3652 | 41 | 0.679 | 0.386 | 1.195 | 0.180 |
| rs831571 | C | 3 | *PSMD6* | 3726 | 1216 | 0.932 | 0.828 | 1.049 | 0.245 | 3726 | 41 | 0.970 | 0.571 | 1.647 | 0.910 |
| rs4607103 | C | 3 | *ADAMTS9-AS2* | 3884 | 1257 | 1.002 | 0.912 | 1.102 | 0.962 | 3884 | 43 | 1.336 | 0.874 | 2.042 | 0.181 |
| rs11708067 | A | 3 | *ADCY5* | 3877 | 1266 | 0.903 | 0.807 | 1.011 | 0.077 | 3877 | 42 | 0.934 | 0.565 | 1.546 | 0.792 |
| rs11920090 | T | 3 | *SLC2A2* | 3606 | 1172 | 1.146 | 0.998 | 1.316 | 0.053 | 3606 | 40 | 2.076 | 0.947 | 4.548 | 0.068 |
| rs4402960 | T | 3 | *IGF2BP2* | 3750 | 1210 | 0.940 | 0.853 | 1.035 | 0.208 | 3750 | 43 | 0.723 | 0.466 | 1.123 | 0.149 |
| rs6815464 | C | 4 | *MAEA* | 3722 | 1218 | 1.061 | 0.926 | 1.214 | 0.394 | 3722 | 41 | 1.502 | 0.751 | 3.005 | 0.250 |
| rs10010131 | G | 4 | *WFS1* | 3843 | 1257 | 1.005 | 0.905 | 1.115 | 0.928 | 3843 | 41 | 1.422 | 0.850 | 2.377 | 0.180 |
| rs459193 | G | 5 | *ANKRD55* | 3884 | 1269 | 1.053 | 0.954 | 1.163 | 0.306 | 3884 | 42 | 0.643 | 0.417 | 0.990 | 0.045 |
| rs4457053 | G | 5 | *ZBED3* | 3579 | 1165 | 0.941 | 0.833 | 1.062 | 0.324 | 3579 | 40 | 0.996 | 0.582 | 1.704 | 0.987 |
| rs7754840 | C | 6 | *CDKAL 1* | 3721 | 1214 | 0.957 | 0.859 | 1.066 | 0.426 | 3721 | 41 | 0.588 | 0.336 | 1.028 | 0.062 |
| rs7756992 | G | 6 | *CDKAL 1* | 3686 | 1205 | 0.959 | 0.860 | 1.069 | 0.450 | 3686 | 41 | 0.711 | 0.418 | 1.208 | 0.207 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs9470794 | C | 6 | *ZFAND3* | 3608 | 1173 | 1.054 | 0.910 | 1.221 | 0.481 | 3608 | 40 | 0.999 | 0.518 | 1.929 | 0.998 |
| rs17168486 | T | 7 | *DGKB* | 3855 | 1249 | 0.983 | 0.887 | 1.090 | 0.749 | 3855 | 43 | 0.621 | 0.372 | 1.039 | 0.070 |
| rs2191349 | T | 7 | *DGKB/TMEM195* | 3903 | 1262 | 0.990 | 0.899 | 1.091 | 0.845 | 3903 | 43 | 1.283 | 0.818 | 2.012 | 0.278 |
| rs864745 | T | 7 | *JAZF1* | 3876 | 1260 | 1.021 | 0.919 | 1.134 | 0.700 | 3876 | 43 | 0.808 | 0.518 | 1.263 | 0.350 |
| rs4607517 | A | 7 | *GCK* | 3903 | 1271 | 1.027 | 0.892 | 1.183 | 0.710 | 3903 | 43 | 0.976 | 0.514 | 1.851 | 0.940 |
| rs17133918 | T | 7 | *GRB10* | 3907 | 1265 | 0.991 | 0.892 | 1.101 | 0.868 | 3907 | 43 | 1.268 | 0.812 | 1.980 | 0.297 |
| rs933360 | A | 7 | *GRB10* | 3905 | 1272 | 1.021 | 0.924 | 1.128 | 0.687 | 3905 | 43 | 1.207 | 0.758 | 1.920 | 0.428 |
| rs6943153 | T | 7 | *GRB10* | 3602 | 1174 | 0.972 | 0.876 | 1.079 | 0.594 | 3602 | 40 | 0.901 | 0.562 | 1.443 | 0.664 |
| rs1799999* | A | 7 | *PP1R3A* | 3890 | 1270 | 0.991 | 0.898 | 1.094 | 0.860 | 3890 | 43 | 0.820 | 0.521 | 1.288 | 0.388 |
| rs6467136 | G | 7 | *GCC1-PAX4* | 3593 | 1163 | 0.954 | 0.868 | 1.048 | 0.329 | 3593 | 39 | 1.912 | 1.168 | 3.128 | 0.010 |
| rs516946 | C | 8 | *ANK1* | 3922 | 1273 | 1.115 | 0.988 | 1.258 | 0.078 | 3922 | 43 | 0.961 | 0.566 | 1.632 | 0.883 |
| rs896854 | T | 8 | *TP53INP1* | 3903 | 1274 | 0.980 | 0.891 | 1.079 | 0.685 | 3903 | 42 | 1.295 | 0.845 | 1.985 | 0.235 |
| rs13266634 | C | 8 | *SLC30A8* | 3898 | 1263 | 0.977 | 0.875 | 1.091 | 0.678 | 3898 | 43 | 0.913 | 0.564 | 1.479 | 0.713 |
| rs7034200 | A | 9 | *GLIS3* | 3868 | 1250 | 1.032 | 0.938 | 1.135 | 0.515 | 3868 | 43 | 1.113 | 0.729 | 1.700 | 0.619 |
| rs10811661 | T | 9 | *CDKN2A/2B* | 3890 | 1259 | 1.083 | 0.940 | 1.248 | 0.271 | 3890 | 43 | 1.271 | 0.639 | 2.527 | 0.494 |
| rs13292136 | C | 9 | *TLE4 (CHCHD9)* | 3706 | 1214 | 0.991 | 0.866 | 1.133 | 0.891 | 3706 | 41 | 0.924 | 0.514 | 1.663 | 0.793 |
| rs2796441 | G | 9 | *TLE 1* | 3905 | 1264 | 1.073 | 0.974 | 1.181 | 0.153 | 3905 | 43 | 0.999 | 0.650 | 1.536 | 0.997 |
| rs12571751 | A | 10 | *ZMIZ1* | 3601 | 1173 | 0.974 | 0.880 | 1.077 | 0.601 | 3601 | 40 | 0.882 | 0.564 | 1.379 | 0.582 |
| rs1111875 | C | 10 | *HHEX* | 3901 | 1265 | 1.044 | 0.949 | 1.150 | 0.377 | 3901 | 43 | 0.831 | 0.537 | 1.286 | 0.406 |
| rs553668 | A | 10 | *ADRA2A* | 3666 | 1197 | 1.058 | 0.953 | 1.175 | 0.293 | 3666 | 39 | 1.024 | 0.636 | 1.651 | 0.921 |
| rs10885122 | G | 10 | *ADRA2A* | 3683 | 1201 | 1.038 | 0.920 | 1.171 | 0.549 | 3683 | 41 | 1.188 | 0.675 | 2.089 | 0.550 |
| rs7903146 | T | 10 | *TCF7L2* | 3543 | 1164 | 1.007 | 0.905 | 1.121 | 0.892 | 3543 | 38 | 1.154 | 0.718 | 1.853 | 0.555 |
| rs689* | A | 11 | *INS,INS-IGF2* | 3903 | 1267 | 1.043 | 0.920 | 1.182 | 0.514 | 3903 | 43 | 1.381 | 0.827 | 2.307 | 0.217 |
| rs163184 | G | 11 | *KCNQ1* | 3713 | 1215 | 1.002 | 0.907 | 1.107 | 0.967 | 3713 | 43 | 1.056 | 0.683 | 1.634 | 0.805 |
| rs2237895 | C | 11 | *KCNQ1* | 3682 | 1200 | 1.013 | 0.918 | 1.117 | 0.799 | 3682 | 40 | 1.199 | 0.775 | 1.855 | 0.415 |
| rs5219 | T | 11 | *KCNJ11* | 3595 | 1179 | 0.990 | 0.897 | 1.094 | 0.848 | 3595 | 40 | 1.274 | 0.827 | 1.964 | 0.272 |
| rs11605924 | A | 11 | *CRY2* | 3909 | 1275 | 1.039 | 0.947 | 1.141 | 0.417 | 3909 | 42 | 1.147 | 0.752 | 1.750 | 0.524 |
| rs7944584 | A | 11 | *MADD* | 3553 | 1168 | 1.081 | 0.954 | 1.226 | 0.222 | 3553 | 38 | 0.993 | 0.564 | 1.749 | 0.981 |
| rs174550 | T | 11 | *FADS1* | 3908 | 1272 | 0.981 | 0.865 | 1.114 | 0.771 | 3908 | 43 | 0.888 | 0.515 | 1.531 | 0.670 |
| rs1552224 | A | 11 | *CENTD2* | 3911 | 1274 | 0.844 | 0.745 | 0.956 | 0.007 | 3911 | 43 | 1.150 | 0.636 | 2.080 | 0.644 |
| rs10830963 | G | 11 | *MTNR1B* | 3714 | 1214 | 0.988 | 0.894 | 1.091 | 0.809 | 3714 | 41 | 0.885 | 0.563 | 1.392 | 0.597 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11063069 | G | 12 | *CCND2* | 3671 | 1203 | 1.028 | 0.899 | 1.176 | 0.687 | 3671 | 40 | 0.552 | 0.255 | 1.195 | 0.132 |
| rs10842994 | C | 12 | *KLHDC5* | 3906 | 1273 | 0.941 | 0.819 | 1.081 | 0.391 | 3906 | 42 | 0.736 | 0.417 | 1.299 | 0.290 |
| rs1153188 | A | 12 | *DCD* | 3912 | 1275 | 1.018 | 0.900 | 1.151 | 0.777 | 3912 | 43 | 1.249 | 0.691 | 2.258 | 0.461 |
| rs1531343 | C | 12 | *HMGA2* | 3915 | 1270 | 0.904 | 0.799 | 1.023 | 0.109 | 3915 | 42 | 0.739 | 0.400 | 1.363 | 0.332 |
| rs7961581 | C | 12 | *TSPAN8,LGR5* | 3703 | 1211 | 1.028 | 0.928 | 1.139 | 0.601 | 3703 | 41 | 1.074 | 0.682 | 1.691 | 0.758 |
| rs35767 | G | 12 | *IGF1* | 3910 | 1275 | 0.960 | 0.857 | 1.076 | 0.488 | 3910 | 43 | 0.787 | 0.483 | 1.280 | 0.334 |
| rs7957197 | T | 12 | *OASL/TCF1/HNF1A* | 3924 | 1274 | 1.016 | 0.837 | 1.232 | 0.876 | 3924 | 43 | 0.789 | 0.365 | 1.709 | 0.548 |
| rs9552911* | A | 13 | *SGCG* | 3890 | 1271 | 1.045 | 0.897 | 1.218 | 0.569 | 3890 | 43 | 1.237 | 0.656 | 2.332 | 0.511 |
| rs17271305 | G | 15 | *VPS13C* | 3825 | 1249 | 0.910 | 0.819 | 1.011 | 0.078 | 3825 | 42 | 0.883 | 0.545 | 1.431 | 0.613 |
| rs11071657 | A | 15 | *FAM148B* | 3897 | 1264 | 0.917 | 0.827 | 1.016 | 0.096 | 3897 | 43 | 0.896 | 0.571 | 1.405 | 0.632 |
| rs7177055 | A | 15 | *HMG20A* | 3907 | 1268 | 0.951 | 0.865 | 1.046 | 0.304 | 3907 | 43 | 1.040 | 0.679 | 1.593 | 0.857 |
| rs11634397 | G | 15 | *ZFAND6* | 3910 | 1268 | 0.974 | 0.884 | 1.073 | 0.593 | 3910 | 43 | 0.942 | 0.612 | 1.450 | 0.786 |
| rs8042680 | A | 15 | *PRC1* | 3887 | 1259 | 0.990 | 0.897 | 1.093 | 0.844 | 3887 | 43 | 0.959 | 0.616 | 1.491 | 0.851 |
| rs9939609 | A | 16 | *FTO* | 3120 | 982 | 1.001 | 0.894 | 1.121 | 0.985 | 3120 | 30 | 1.196 | 0.710 | 2.014 | 0.502 |
| rs7202877 | T | 16 | *BCAR1* | 3915 | 1275 | 1.059 | 0.884 | 1.269 | 0.534 | 3915 | 43 | 1.577 | 0.587 | 4.242 | 0.366 |
| rs8090011 | G | 18 | *LAMA1* | 3911 | 1267 | 0.934 | 0.849 | 1.027 | 0.160 | 3911 | 43 | 1.181 | 0.771 | 1.809 | 0.444 |
| rs10401969 | C | 19 | *SUGP1* | 3605 | 1172 | 0.830 | 0.700 | 0.983 | 0.031 | 3605 | 40 | 0.591 | 0.238 | 1.467 | 0.257 |
| rs8108269 | G | 19 | *GIPR* | 3508 | 1129 | 1.044 | 0.938 | 1.162 | 0.426 | 3508 | 40 | 1.025 | 0.642 | 1.637 | 0.916 |
| rs10423928 | A | 19 | *GIPR* | 3911 | 1272 | 1.068 | 0.935 | 1.219 | 0.332 | 3911 | 42 | 0.530 | 0.245 | 1.146 | 0.107 |
| rs6017317 | G | 20 | *FITM2-R3HDML-HNF4A* | 3758 | 1224 | 0.968 | 0.875 | 1.072 | 0.535 | 3758 | 42 | 0.906 | 0.575 | 1.429 | 0.672 |
| rs5945326 | A | X | *DUSP9* | 3589 | 1163 | 1.017 | 0.919 | 1.125 | 0.745 | 3589 | 39 | 1.075 | 0.680 | 1.698 | 0.757 |
| rs4812829* | A | 20 | *HNF4A* | 3801 | 1236 | 0.97 | 0.88 | 1.08 | 0.63 | 3801 | 42 | 1.260 | 0.790 | 1.980 | 0.320 |
| rs7178572* | G | 15 | *HMG20A* | 3541 | 1140 | 0.99 | 0.9 | 1.1 | 0.93 | 3541 | 38 | 0.970 | 0.610 | 1.520 | 0.900 |

| | | | | PPBS = 7,8 | | | | | | PPBS = 8,5 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | effect allele | Chr | Locus | n | n_cases | OR | CI(lower) | CI(upper) | pval | n | n_cases | OR | CI(lower) | CI(upper) | pval |
| rs2296172 | G | 1 | *MACF1* | 3847 | 317 | 0.929 | 0.713 | 1.210 | 0.584 | 3847 | 170 | 0.953 | 0.670 | 1.355 | 0.787 |
| rs340874 | C | 1 | *PROX1* | 3709 | 306 | 0.931 | 0.790 | 1.096 | 0.389 | 3709 | 162 | 0.914 | 0.734 | 1.139 | 0.423 |
| rs7578597 | T | 2 | *THADA* | 3710 | 307 | 0.887 | 0.705 | 1.117 | 0.308 | 3710 | 164 | 0.770 | 0.574 | 1.034 | 0.082 |
| rs243088 | T | 2 | *BCL 11A* | 3717 | 308 | 1.090 | 0.923 | 1.287 | 0.311 | 3717 | 165 | 1.203 | 0.963 | 1.503 | 0.103 |
| rs998451* | A | 2 | *TMEM163* | 3882 | 319 | 0.984 | 0.788 | 1.228 | 0.886 | 3882 | 171 | 0.897 | 0.659 | 1.219 | 0.486 |
| rs7593730 | T | 2 | *RBMS1/ITGB6* | 3906 | 322 | 1.003 | 0.824 | 1.220 | 0.978 | 3906 | 172 | 0.919 | 0.702 | 1.202 | 0.537 |
| rs7607980 | C | 2 | *COBL1* | 3885 | 320 | 0.984 | 0.756 | 1.280 | 0.901 | 3885 | 172 | 1.262 | 0.912 | 1.747 | 0.160 |
| rs13389219 | C | 2 | *GRB14* | 3829 | 315 | 1.249 | 1.031 | 1.512 | 0.023 | 3829 | 168 | 1.164 | 0.904 | 1.500 | 0.239 |
| rs560887 | C | 2 | *G6PC2/ABCB11* | 3910 | 322 | 1.134 | 0.881 | 1.460 | 0.329 | 3910 | 172 | 0.927 | 0.676 | 1.272 | 0.639 |
| rs7578326 | A | 2 | *KIAA1486/IRS1* | 3600 | 296 | 0.930 | 0.764 | 1.132 | 0.470 | 3600 | 160 | 0.973 | 0.747 | 1.267 | 0.838 |
| rs2943641 | C | 2 | *IRS1* | 3643 | 298 | 0.901 | 0.746 | 1.089 | 0.281 | 3643 | 160 | 0.906 | 0.704 | 1.165 | 0.441 |
| rs4675095 | A | 2 | *IRS1* | 3817 | 313 | 1.119 | 0.871 | 1.437 | 0.379 | 3817 | 167 | 1.203 | 0.852 | 1.699 | 0.293 |
| rs1801282 | C | 3 | *PPARG* | 3652 | 304 | 0.898 | 0.708 | 1.139 | 0.374 | 3652 | 163 | 1.007 | 0.725 | 1.400 | 0.966 |
| rs831571 | C | 3 | *PSMD6* | 3726 | 309 | 1.060 | 0.864 | 1.300 | 0.579 | 3726 | 165 | 1.212 | 0.911 | 1.611 | 0.186 |
| rs4607103 | C | 3 | *ADAMTS9-AS2* | 3884 | 315 | 1.104 | 0.939 | 1.297 | 0.230 | 3884 | 169 | 1.123 | 0.905 | 1.394 | 0.293 |
| rs11708067 | A | 3 | *ADCY5* | 3877 | 320 | 0.953 | 0.787 | 1.153 | 0.618 | 3877 | 171 | 0.895 | 0.696 | 1.152 | 0.390 |
| rs11920090 | T | 3 | *SLC2A2* | 3606 | 299 | 1.179 | 0.927 | 1.500 | 0.181 | 3606 | 162 | 1.457 | 1.032 | 2.056 | 0.032 |
| rs4402960 | T | 3 | *IGF2BP2* | 3750 | 307 | 1.049 | 0.891 | 1.235 | 0.563 | 3750 | 168 | 1.004 | 0.809 | 1.247 | 0.968 |
| rs6815464 | C | 4 | *MAEA* | 3722 | 307 | 1.036 | 0.822 | 1.305 | 0.767 | 3722 | 165 | 0.924 | 0.685 | 1.246 | 0.605 |
| rs10010131 | G | 4 | *WFS1* | 3843 | 315 | 1.120 | 0.934 | 1.343 | 0.222 | 3843 | 168 | 1.110 | 0.870 | 1.416 | 0.402 |
| rs459193 | G | 5 | *ANKRD55* | 3884 | 318 | 1.007 | 0.850 | 1.192 | 0.940 | 3884 | 169 | 1.066 | 0.848 | 1.340 | 0.585 |
| rs4457053 | G | 5 | *ZBED3* | 3579 | 297 | 1.082 | 0.885 | 1.324 | 0.440 | 3579 | 162 | 1.157 | 0.891 | 1.504 | 0.274 |
| rs7754840 | C | 6 | *CDKAL 1* | 3721 | 307 | 0.900 | 0.746 | 1.084 | 0.267 | 3721 | 163 | 0.936 | 0.729 | 1.201 | 0.602 |
| rs7756992 | G | 6 | *CDKAL 1* | 3686 | 305 | 0.935 | 0.776 | 1.128 | 0.484 | 3686 | 163 | 0.946 | 0.737 | 1.215 | 0.665 |
| rs9470794 | C | 6 | *ZFAND3* | 3608 | 299 | 1.082 | 0.848 | 1.382 | 0.525 | 3608 | 163 | 0.920 | 0.653 | 1.296 | 0.633 |
| rs17168486 | T | 7 | *DGKB* | 3855 | 314 | 0.996 | 0.836 | 1.187 | 0.965 | 3855 | 169 | 0.824 | 0.646 | 1.052 | 0.121 |
| rs2191349 | T | 7 | *DGKB/TMEM195* | 3903 | 320 | 1.074 | 0.909 | 1.268 | 0.404 | 3903 | 172 | 1.138 | 0.909 | 1.425 | 0.259 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs864745 | T | 7 | *JAZF1* | 3876 | 316 | 0.978 | 0.818 | 1.168 | 0.803 | 3876 | 170 | 0.976 | 0.770 | 1.238 | 0.844 |
| rs4607517 | A | 7 | *GCK* | 3903 | 322 | 1.082 | 0.854 | 1.369 | 0.514 | 3903 | 172 | 0.929 | 0.667 | 1.294 | 0.662 |
| rs17133918 | T | 7 | *GRB10* | 3907 | 318 | 1.021 | 0.854 | 1.221 | 0.819 | 3907 | 172 | 1.063 | 0.840 | 1.346 | 0.612 |
| rs933360 | A | 7 | *GRB10* | 3905 | 322 | 1.014 | 0.856 | 1.202 | 0.871 | 3905 | 173 | 1.108 | 0.880 | 1.395 | 0.381 |
| rs6943153 | T | 7 | *GRB10* | 3602 | 298 | 0.880 | 0.735 | 1.053 | 0.161 | 3602 | 163 | 0.775 | 0.608 | 0.989 | 0.040 |
| rs1799999* | A | 7 | *PP1R3A* | 3890 | 320 | 0.851 | 0.718 | 1.009 | 0.063 | 3890 | 173 | 0.850 | 0.677 | 1.067 | 0.161 |
| rs6467136 | G | 7 | *GCC1-PAX4* | 3593 | 303 | 1.115 | 0.949 | 1.310 | 0.184 | 3593 | 162 | 1.253 | 1.006 | 1.561 | 0.044 |
| rs516946 | C | 8 | *ANK1* | 3922 | 325 | 1.038 | 0.847 | 1.273 | 0.717 | 3922 | 173 | 0.993 | 0.758 | 1.300 | 0.957 |
| rs896854 | T | 8 | *TP53INP1* | 3903 | 320 | 0.942 | 0.799 | 1.110 | 0.477 | 3903 | 171 | 0.906 | 0.726 | 1.131 | 0.384 |
| rs13266634 | C | 8 | *SLC30A8* | 3898 | 319 | 0.954 | 0.792 | 1.150 | 0.623 | 3898 | 171 | 0.980 | 0.762 | 1.259 | 0.873 |
| rs7034200 | A | 9 | *GLIS3* | 3868 | 315 | 0.982 | 0.834 | 1.155 | 0.822 | 3868 | 169 | 0.875 | 0.704 | 1.088 | 0.230 |
| rs10811661 | T | 9 | *CDKN2A/2B* | 3890 | 316 | 0.973 | 0.767 | 1.234 | 0.821 | 3890 | 170 | 1.092 | 0.785 | 1.518 | 0.603 |
| rs13292136 | C | 9 | *TLE4 (CHCHD9)* | 3706 | 304 | 0.938 | 0.749 | 1.175 | 0.578 | 3706 | 164 | 0.994 | 0.732 | 1.350 | 0.972 |
| rs2796441 | G | 9 | *TLE 1* | 3905 | 320 | 0.994 | 0.844 | 1.171 | 0.945 | 3905 | 172 | 0.998 | 0.802 | 1.242 | 0.987 |
| rs12571751 | A | 10 | *ZMIZ1* | 3601 | 299 | 0.874 | 0.737 | 1.036 | 0.121 | 3601 | 163 | 0.900 | 0.717 | 1.128 | 0.359 |
| rs1111875 | C | 10 | *HHEX* | 3901 | 316 | 0.921 | 0.781 | 1.087 | 0.331 | 3901 | 170 | 1.074 | 0.862 | 1.337 | 0.525 |
| rs553668 | A | 10 | *ADRA2A* | 3666 | 301 | 1.162 | 0.976 | 1.385 | 0.092 | 3666 | 163 | 1.184 | 0.939 | 1.493 | 0.154 |
| rs10885122 | G | 10 | *ADRA2A* | 3683 | 303 | 1.020 | 0.831 | 1.253 | 0.849 | 3683 | 160 | 1.031 | 0.781 | 1.361 | 0.828 |
| rs7903146 | T | 10 | *TCF7L2* | 3543 | 293 | 1.123 | 0.938 | 1.343 | 0.206 | 3543 | 156 | 1.257 | 0.992 | 1.593 | 0.058 |
| rs689* | A | 11 | *INS,INS-IGF2* | 3903 | 319 | 1.099 | 0.891 | 1.355 | 0.377 | 3903 | 172 | 1.082 | 0.817 | 1.432 | 0.582 |
| rs163184 | G | 11 | *KCNQ1* | 3713 | 307 | 0.897 | 0.758 | 1.061 | 0.204 | 3713 | 165 | 0.888 | 0.710 | 1.112 | 0.300 |
| rs2237895 | C | 11 | *KCNQ1* | 3682 | 304 | 0.959 | 0.812 | 1.133 | 0.623 | 3682 | 161 | 0.895 | 0.714 | 1.122 | 0.337 |
| rs5219 | T | 11 | *KCNJ11* | 3595 | 301 | 1.176 | 0.997 | 1.387 | 0.055 | 3595 | 160 | 1.116 | 0.893 | 1.394 | 0.335 |
| rs11605924 | A | 11 | *CRY2* | 3909 | 318 | 0.832 | 0.709 | 0.976 | 0.024 | 3909 | 169 | 0.785 | 0.632 | 0.974 | 0.028 |
| rs7944584 | A | 11 | *MADD* | 3553 | 294 | 0.909 | 0.739 | 1.117 | 0.364 | 3553 | 157 | 1.049 | 0.787 | 1.399 | 0.743 |
| rs174550 | T | 11 | *FADS1* | 3908 | 322 | 0.975 | 0.787 | 1.208 | 0.819 | 3908 | 172 | 0.920 | 0.694 | 1.219 | 0.561 |
| rs1552224 | A | 11 | *CENTD2* | 3911 | 323 | 0.917 | 0.743 | 1.132 | 0.420 | 3911 | 173 | 0.983 | 0.737 | 1.310 | 0.906 |
| rs10830963 | G | 11 | *MTNR1B* | 3714 | 305 | 0.897 | 0.755 | 1.066 | 0.217 | 3714 | 162 | 0.926 | 0.735 | 1.166 | 0.514 |
| rs11063069 | G | 12 | *CCND2* | 3671 | 305 | 1.000 | 0.795 | 1.258 | 0.998 | 3671 | 164 | 0.846 | 0.612 | 1.171 | 0.314 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs10842994 | C | 12 | *KLHDC5* | 3906 | 321 | 1.163 | 0.904 | 1.495 | 0.240 | 3906 | 171 | 1.070 | 0.771 | 1.486 | 0.685 |
| rs1153188 | A | 12 | *DCD* | 3912 | 323 | 1.179 | 0.947 | 1.467 | 0.141 | 3912 | 173 | 1.010 | 0.763 | 1.337 | 0.942 |
| rs1531343 | C | 12 | *HMGA2* | 3915 | 321 | 0.839 | 0.674 | 1.044 | 0.115 | 3915 | 170 | 0.920 | 0.690 | 1.226 | 0.568 |
| rs7961581 | C | 12 | *TSPAN8,LGR5* | 3703 | 304 | 0.892 | 0.747 | 1.066 | 0.209 | 3703 | 163 | 0.878 | 0.691 | 1.115 | 0.286 |
| rs35767 | G | 12 | *IGF1* | 3910 | 322 | 0.909 | 0.752 | 1.100 | 0.329 | 3910 | 172 | 0.958 | 0.740 | 1.240 | 0.746 |
| rs7957197 | T | 12 | *OASL/TCF1/HNF1A* | 3924 | 325 | 0.852 | 0.627 | 1.157 | 0.304 | 3924 | 173 | 0.958 | 0.624 | 1.471 | 0.845 |
| rs9552911* | A | 13 | *SGCG* | 3890 | 317 | 1.048 | 0.811 | 1.356 | 0.719 | 3890 | 169 | 0.880 | 0.609 | 1.272 | 0.497 |
| rs17271305 | G | 15 | *VPS13C* | 3825 | 317 | 1.031 | 0.864 | 1.230 | 0.735 | 3825 | 169 | 0.969 | 0.763 | 1.231 | 0.794 |
| rs11071657 | A | 15 | *FAM148B* | 3897 | 318 | 1.035 | 0.867 | 1.235 | 0.705 | 3897 | 170 | 1.105 | 0.869 | 1.404 | 0.416 |
| rs7177055 | A | 15 | *HMG20A* | 3907 | 319 | 1.013 | 0.862 | 1.192 | 0.873 | 3907 | 171 | 1.223 | 0.982 | 1.522 | 0.072 |
| rs11634397 | G | 15 | *ZFAND6* | 3910 | 321 | 0.881 | 0.748 | 1.038 | 0.129 | 3910 | 170 | 0.919 | 0.737 | 1.145 | 0.451 |
| rs8042680 | A | 15 | *PRC1* | 3887 | 317 | 0.880 | 0.744 | 1.040 | 0.134 | 3887 | 170 | 0.894 | 0.715 | 1.119 | 0.329 |
| rs9939609 | A | 16 | *FTO* | 3120 | 219 | 1.028 | 0.838 | 1.261 | 0.794 | 3120 | 127 | 0.841 | 0.639 | 1.107 | 0.218 |
| rs7202877 | T | 16 | *BCAR1* | 3915 | 322 | 1.181 | 0.854 | 1.635 | 0.315 | 3915 | 173 | 0.918 | 0.620 | 1.359 | 0.669 |
| rs8090011 | G | 18 | *LAMA1* | 3911 | 320 | 0.926 | 0.787 | 1.089 | 0.353 | 3911 | 172 | 0.942 | 0.758 | 1.170 | 0.587 |
| rs10401969 | C | 19 | *SUGP1* | 3605 | 298 | 1.006 | 0.760 | 1.333 | 0.964 | 3605 | 161 | 1.102 | 0.767 | 1.584 | 0.598 |
| rs8108269 | G | 19 | *GIPR* | 3508 | 302 | 1.024 | 0.857 | 1.222 | 0.795 | 3508 | 159 | 1.128 | 0.890 | 1.428 | 0.319 |
| rs10423928 | A | 19 | *GIPR* | 3911 | 321 | 0.898 | 0.711 | 1.136 | 0.370 | 3911 | 171 | 0.863 | 0.626 | 1.188 | 0.366 |
| rs6017317 | G | 20 | *FITM2-R3HDML-HNF4A* | 3758 | 315 | 0.948 | 0.798 | 1.126 | 0.543 | 3758 | 165 | 1.129 | 0.898 | 1.420 | 0.298 |
| rs5945326 | A | X | *DUSP9* | 3589 | 296 | 0.951 | 0.803 | 1.127 | 0.561 | 3589 | 159 | 0.902 | 0.720 | 1.130 | 0.370 |
| rs4812829* | A | 20 | *HNF4A* | 3801 | 317 | 0.99 | 0.82 | 1.18 | 0.88 | 3801 | 170 | 1.050 | 0.830 | 1.330 | 0.700 |
| rs7178572* | G | 15 | *HMG20A* | 3541 | 279 | 0.99 | 0.83 | 1.18 | 0.93 | 3541 | 153 | 1.210 | 0.960 | 1.520 | 0.100 |

| | | | | FBS5,1 AND PPBS =8,5 | | | | | | FBS7,0 AND PPBS =7,8 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | effect allele | Chr | Locus | n | n_cases | OR | CI(lower) | CI(upper) | pval | n | n_cases | OR | CI(lower) | CI(upper) | pval |
| rs2296172 | G | 1 | *MACF1* | 3847 | 96 | 0.958 | 0.603 | 1.523 | 0.856 | 3847 | 27 | 0.772 | 0.304 | 1.959 | 0.585 |
| rs340874 | C | 1 | *PROX1* | 3709 | 92 | 0.897 | 0.672 | 1.197 | 0.460 | 3709 | 25 | 0.917 | 0.532 | 1.583 | 0.757 |
| rs7578597 | T | 2 | *THADA* | 3710 | 93 | 0.727 | 0.498 | 1.061 | 0.099 | 3710 | 25 | 0.744 | 0.360 | 1.538 | 0.425 |
| rs243088 | T | 2 | *BCL 11A* | 3717 | 94 | 0.996 | 0.744 | 1.334 | 0.980 | 3717 | 26 | 0.931 | 0.535 | 1.620 | 0.801 |
| rs998451* | A | 2 | *TMEM163* | 3882 | 98 | 0.749 | 0.487 | 1.153 | 0.190 | 3882 | 26 | 0.735 | 0.318 | 1.700 | 0.472 |
| rs7593730 | T | 2 | *RBMS1/ITGB6* | 3906 | 97 | 0.999 | 0.706 | 1.413 | 0.997 | 3906 | 27 | 1.128 | 0.597 | 2.131 | 0.710 |
| rs7607980 | C | 2 | *COBL1* | 3885 | 97 | 1.325 | 0.869 | 2.019 | 0.191 | 3885 | 27 | 0.809 | 0.317 | 2.070 | 0.659 |
| rs13389219 | C | 2 | *GRB14* | 3829 | 93 | 1.011 | 0.728 | 1.402 | 0.950 | 3829 | 24 | 0.834 | 0.449 | 1.549 | 0.566 |
| rs560887 | C | 2 | *G6PC2/ABCB11* | 3910 | 97 | 0.871 | 0.581 | 1.306 | 0.503 | 3910 | 27 | 1.757 | 0.645 | 4.785 | 0.271 |
| rs7578326 | A | 2 | *KIAA1486/IRS1* | 3600 | 89 | 0.809 | 0.579 | 1.130 | 0.213 | 3600 | 24 | 0.600 | 0.329 | 1.092 | 0.095 |
| rs2943641 | C | 2 | *IRS1* | 3643 | 90 | 0.813 | 0.588 | 1.125 | 0.211 | 3643 | 24 | 0.622 | 0.345 | 1.122 | 0.115 |
| rs4675095 | A | 2 | *IRS1* | 3817 | 93 | 1.092 | 0.703 | 1.699 | 0.695 | 3817 | 25 | 0.808 | 0.380 | 1.721 | 0.581 |
| rs1801282 | C | 3 | *PPARG* | 3652 | 93 | 1.028 | 0.665 | 1.588 | 0.901 | 3652 | 26 | 0.843 | 0.395 | 1.801 | 0.660 |
| rs831571 | C | 3 | *PSMD6* | 3726 | 94 | 1.393 | 0.942 | 2.061 | 0.097 | 3726 | 26 | 1.317 | 0.638 | 2.718 | 0.457 |
| rs4607103 | C | 3 | *ADAMTS9-AS2* | 3884 | 96 | 1.226 | 0.922 | 1.630 | 0.160 | 3884 | 27 | 0.984 | 0.579 | 1.674 | 0.954 |
| rs11708067 | A | 3 | *ADCY5* | 3877 | 95 | 0.995 | 0.706 | 1.402 | 0.978 | 3877 | 26 | 0.661 | 0.367 | 1.193 | 0.169 |
| rs11920090 | T | 3 | *SLC2A2* | 3606 | 91 | 1.607 | 1.001 | 2.580 | 0.050 | 3606 | 24 | 3.025 | 0.931 | 9.827 | 0.066 |
| rs4402960 | T | 3 | *IGF2BP2* | 375 | 93 | 0.92 | 0.693 | 1.239 | 0.60 | 3750 | 27 | 0.77 | 0.447 | 1.338 | 0.358 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 0 | | 6 | | | 5 | | | 3 | | | |
| rs6815464 | C | 4 | *MAEA* | 3722 | 94 | 1.098 | 0.727 | 1.657 | 0.657 | 3722 | 26 | 1.753 | 0.700 | 4.394 | 0.231 |
| rs10010131 | G | 4 | *WFS1* | 3843 | 93 | 1.270 | 0.910 | 1.772 | 0.160 | 3843 | 25 | 1.365 | 0.714 | 2.613 | 0.347 |
| rs459193 | G | 5 | *ANKRD55* | 3884 | 95 | 0.935 | 0.695 | 1.257 | 0.654 | 3884 | 26 | 0.589 | 0.341 | 1.019 | 0.058 |
| rs4457053 | G | 5 | *ZBED3* | 3579 | 91 | 1.143 | 0.808 | 1.617 | 0.449 | 3579 | 24 | 1.235 | 0.643 | 2.373 | 0.527 |
| rs7754840 | C | 6 | *CDKAL 1* | 3721 | 92 | 0.824 | 0.586 | 1.157 | 0.263 | 3721 | 26 | 0.626 | 0.315 | 1.243 | 0.181 |
| rs7756992 | G | 6 | *CDKAL 1* | 3686 | 92 | 0.776 | 0.548 | 1.098 | 0.152 | 3686 | 26 | 0.817 | 0.431 | 1.550 | 0.537 |
| rs9470794 | C | 6 | *ZFAND3* | 3608 | 92 | 0.856 | 0.538 | 1.362 | 0.511 | 3608 | 24 | 0.995 | 0.428 | 2.318 | 0.991 |
| rs17168486 | T | 7 | *DGKB* | 3855 | 94 | 0.775 | 0.558 | 1.078 | 0.130 | 3855 | 27 | 0.476 | 0.235 | 0.964 | 0.039 |
| rs2191349 | T | 7 | *DGKB/TMEM195* | 3903 | 97 | 1.118 | 0.832 | 1.502 | 0.460 | 3903 | 27 | 2.181 | 1.149 | 4.140 | 0.017 |
| rs864745 | T | 7 | *JAZF1* | 3876 | 96 | 0.946 | 0.693 | 1.290 | 0.724 | 3876 | 27 | 0.667 | 0.387 | 1.147 | 0.143 |
| rs4607517 | A | 7 | *GCK* | 3903 | 96 | 1.000 | 0.652 | 1.535 | 0.998 | 3903 | 27 | 1.338 | 0.648 | 2.762 | 0.431 |
| rs17133918 | T | 7 | *GRB10* | 3907 | 97 | 1.266 | 0.938 | 1.709 | 0.124 | 3907 | 27 | 1.204 | 0.684 | 2.121 | 0.519 |
| rs933360 | A | 7 | *GRB10* | 3905 | 98 | 1.077 | 0.796 | 1.458 | 0.630 | 3905 | 27 | 1.067 | 0.602 | 1.890 | 0.825 |
| rs6943153 | T | 7 | *GRB10* | 3602 | 92 | 0.770 | 0.558 | 1.063 | 0.112 | 3602 | 24 | 1.035 | 0.571 | 1.874 | 0.911 |
| rs1799999* | A | 7 | *PP1R3A* | 3890 | 99 | 0.711 | 0.522 | 0.966 | 0.029 | 3890 | 27 | 0.678 | 0.376 | 1.223 | 0.197 |
| rs6467136 | G | 7 | *GCC1-PAX4* | 3593 | 91 | 1.202 | 0.901 | 1.604 | 0.212 | 3593 | 25 | 2.698 | 1.350 | 5.392 | 0.005 |
| rs516946 | C | 8 | *ANK1* | 3922 | 97 | 1.130 | 0.780 | 1.638 | 0.518 | 3922 | 27 | 1.276 | 0.617 | 2.640 | 0.511 |
| rs896854 | T | 8 | *TP53INP1* | 3903 | 95 | 0.910 | 0.679 | 1.220 | 0.528 | 3903 | 26 | 1.048 | 0.608 | 1.807 | 0.866 |
| rs13266634 | C | 8 | *SLC30A8* | 3898 | 96 | 1.014 | 0.725 | 1.417 | 0.937 | 3898 | 27 | 0.759 | 0.425 | 1.358 | 0.353 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs7034200 | A | 9 | *GLIS3* | 3868 | 96 | 0.797 | 0.599 | 1.060 | 0.118 | 3868 | 27 | 1.153 | 0.676 | 1.965 | 0.601 |
| rs10811661 | T | 9 | *CDKN2A/2B* | 3890 | 95 | 1.082 | 0.699 | 1.673 | 0.724 | 3890 | 27 | 1.184 | 0.510 | 2.751 | 0.694 |
| rs13292136 | C | 9 | *TLE4 (CHCHD9)* | 3706 | 93 | 1.074 | 0.710 | 1.624 | 0.734 | 3706 | 26 | 0.829 | 0.407 | 1.687 | 0.605 |
| rs2796441 | G | 9 | *TLE 1* | 3905 | 97 | 0.983 | 0.737 | 1.311 | 0.908 | 3905 | 27 | 1.024 | 0.595 | 1.760 | 0.933 |
| rs12571751 | A | 10 | *ZMIZ1* | 3601 | 92 | 0.901 | 0.670 | 1.212 | 0.490 | 3601 | 24 | 0.986 | 0.552 | 1.759 | 0.962 |
| rs1111875 | C | 10 | *HHEX* | 3901 | 97 | 0.993 | 0.744 | 1.325 | 0.962 | 3901 | 27 | 0.947 | 0.549 | 1.632 | 0.843 |
| rs553668 | A | 10 | *ADRA2A* | 3666 | 90 | 1.117 | 0.818 | 1.525 | 0.488 | 3666 | 24 | 0.808 | 0.427 | 1.529 | 0.512 |
| rs10885122 | G | 10 | *ADRA2A* | 3683 | 91 | 0.940 | 0.658 | 1.342 | 0.732 | 3683 | 26 | 1.111 | 0.555 | 2.227 | 0.766 |
| rs7903146 | T | 10 | *TCF7L2* | 3543 | 89 | 1.369 | 1.008 | 1.859 | 0.045 | 3543 | 24 | 1.243 | 0.690 | 2.239 | 0.470 |
| rs689* | A | 11 | *INS,INS-IGF2* | 3903 | 97 | 1.227 | 0.860 | 1.752 | 0.260 | 3903 | 27 | 1.886 | 1.037 | 3.432 | 0.038 |
| rs163184 | G | 11 | *KCNQ1* | 3713 | 95 | 0.823 | 0.614 | 1.104 | 0.193 | 3713 | 27 | 1.072 | 0.618 | 1.858 | 0.805 |
| rs2237895 | C | 11 | *KCNQ1* | 3682 | 92 | 0.819 | 0.607 | 1.105 | 0.192 | 3682 | 25 | 1.283 | 0.741 | 2.222 | 0.374 |
| rs5219 | T | 11 | *KCNJ11* | 3595 | 89 | 1.111 | 0.827 | 1.492 | 0.486 | 3595 | 25 | 0.962 | 0.550 | 1.684 | 0.892 |
| rs11605924 | A | 11 | *CRY2* | 3909 | 95 | 0.864 | 0.650 | 1.147 | 0.312 | 3909 | 26 | 1.223 | 0.715 | 2.092 | 0.463 |
| rs7944584 | A | 11 | *MADD* | 3553 | 91 | 0.960 | 0.667 | 1.381 | 0.824 | 3553 | 24 | 0.930 | 0.462 | 1.870 | 0.838 |
| rs174550 | T | 11 | *FADS1* | 3908 | 97 | 1.023 | 0.698 | 1.500 | 0.907 | 3908 | 27 | 1.182 | 0.557 | 2.507 | 0.663 |
| rs1552224 | A | 11 | *CENTD2* | 3911 | 98 | 1.412 | 0.924 | 2.157 | 0.111 | 3911 | 27 | 1.183 | 0.557 | 2.513 | 0.661 |
| rs10830963 | G | 11 | *MTNR1B* | 3714 | 93 | 1.064 | 0.791 | 1.432 | 0.681 | 3714 | 26 | 0.959 | 0.547 | 1.682 | 0.885 |
| rs11063069 | G | 12 | *CCND2* | 3671 | 93 | 0.610 | 0.376 | 0.992 | 0.046 | 3671 | 26 | 0.350 | 0.109 | 1.121 | 0.077 |
| rs10842994 | C | 12 | *KLHDC5* | 3906 | 96 | 0.858 | 0.575 | 1.280 | 0.453 | 3906 | 26 | 0.705 | 0.346 | 1.437 | 0.336 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs1153188 | A | 12 | *DCD* | 3912 | 98 | 1.052 | 0.725 | 1.529 | 0.788 | 3912 | 27 | 1.798 | 0.768 | 4.212 | 0.177 |
| rs1531343 | C | 12 | *HMGA2* | 3915 | 96 | 0.882 | 0.601 | 1.294 | 0.520 | 3915 | 26 | 0.697 | 0.315 | 1.545 | 0.374 |
| rs7961581 | C | 12 | *TSPAN8,LGR5* | 3703 | 93 | 0.800 | 0.581 | 1.101 | 0.171 | 3703 | 26 | 0.869 | 0.482 | 1.567 | 0.640 |
| rs35767 | G | 12 | *IGF1* | 3910 | 98 | 1.301 | 0.900 | 1.880 | 0.162 | 3910 | 27 | 1.012 | 0.526 | 1.946 | 0.971 |
| rs7957197 | T | 12 | *OASL/TCF1/HNF1A* | 3924 | 97 | 1.027 | 0.571 | 1.848 | 0.930 | 3924 | 27 | 0.579 | 0.248 | 1.355 | 0.208 |
| rs9552911* | A | 13 | *SGCG* | 3890 | 97 | 1.031 | 0.653 | 1.626 | 0.896 | 3890 | 27 | 1.257 | 0.567 | 2.787 | 0.574 |
| rs17271305 | G | 15 | *VPS13C* | 3825 | 93 | 0.795 | 0.568 | 1.111 | 0.179 | 3825 | 26 | 0.919 | 0.501 | 1.685 | 0.784 |
| rs11071657 | A | 15 | *FAM148B* | 3897 | 96 | 1.105 | 0.805 | 1.516 | 0.537 | 3897 | 27 | 0.867 | 0.494 | 1.520 | 0.618 |
| rs7177055 | A | 15 | *HMG20A* | 3907 | 96 | 1.044 | 0.783 | 1.391 | 0.770 | 3907 | 27 | 1.219 | 0.709 | 2.096 | 0.475 |
| rs11634397 | G | 15 | *ZFAND6* | 3910 | 94 | 0.937 | 0.699 | 1.258 | 0.667 | 3910 | 27 | 0.824 | 0.480 | 1.413 | 0.482 |
| rs8042680 | A | 15 | *PRC1* | 3887 | 95 | 0.772 | 0.577 | 1.034 | 0.083 | 3887 | 27 | 0.832 | 0.480 | 1.441 | 0.511 |
| rs9939609 | A | 16 | *FTO* | 3120 | 68 | 0.836 | 0.575 | 1.216 | 0.349 | 3120 | 21 | 1.120 | 0.596 | 2.103 | 0.726 |
| rs7202877 | T | 16 | *BCAR1* | 3915 | 98 | 0.939 | 0.558 | 1.581 | 0.814 | 3915 | 27 | 1.323 | 0.422 | 4.148 | 0.631 |
| rs8090011 | G | 18 | *LAMA1* | 3911 | 97 | 0.947 | 0.712 | 1.261 | 0.711 | 3911 | 27 | 0.949 | 0.556 | 1.620 | 0.848 |
| rs10401969 | C | 19 | *SUGP1* | 3605 | 91 | 0.916 | 0.552 | 1.520 | 0.735 | 3605 | 24 | 0.807 | 0.289 | 2.253 | 0.682 |
| rs8108269 | G | 19 | *GIPR* | 3508 | 90 | 0.919 | 0.667 | 1.265 | 0.603 | 3508 | 25 | 0.989 | 0.546 | 1.790 | 0.971 |
| rs10423928 | A | 19 | *GIPR* | 3911 | 95 | 0.806 | 0.521 | 1.248 | 0.335 | 3911 | 26 | 0.755 | 0.324 | 1.759 | 0.515 |
| rs6017317 | G | 20 | *FITM2-R3HDML-HNF4A* | 3758 | 94 | 1.089 | 0.806 | 1.470 | 0.578 | 3758 | 27 | 0.751 | 0.419 | 1.345 | 0.335 |
| rs5945326 | A | X | *DUSP9* | 3589 | 89 | 0.834 | 0.620 | 1.124 | 0.233 | 3589 | 23 | 1.078 | 0.594 | 1.956 | 0.804 |
| rs4812829* | A | 20 | *HNF4A* | 3801 | 97 | 0.97 | 0.7 | 1.32 | 0.83 | 3801 | 27 | 0.8 | 0.43 | 1.49 | 0.49 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs7178572* | G | 15 | *HMG20A* | 3541 | 81 | 1.15 | 0.84 | 1.58 | 0.37 | 3541 | 22 | 1 | 0.56 | 1.83 | 0.98 |

# Paper IV

# Phenotypic and genotypic differences between Indian and Swedish women with gestational diabetes mellitus

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## Abstract

**Introduction**: Gestational diabetes mellitus is a transient form of diabetes characterized by impaired insulin secretion and action during pregnancy. Population based differences in prevalence exist which could be explained by phenotypic and genetic differences. The aim of this study was to examine these differences in pregnant women from India and Sweden.

**Methods**: 4018 unrelated pregnant women from India and 507 women from Sweden were examined for differences in insulin secretion and insulin sensitivity. Six SNPs associated with GDM / T2D in Indian populations and 79 SNPs associated with GDM /T2D in European populations were assessed for association with GDM in Indian and Swedish women.

**Results**: Indian women had higher prevalence of GDM (compared to previous reports), lower insulin secretion and better insulin sensitivity than Swedish women. The rs7178572 SNP in the *HMG20A* gene previously associated with T2D in Indian and GDM in South Indian populations nominally associated with GDM in Indian but not in Swedish women. The T2D risk SNP rs11605924 in the *CRY2* gene was associated with GDM in both populations, but in opposite directions; the T2D risk variant was associated with increased risk of GDM in Swedish but decreased risk in Indian women. No overlap was seen between GDM risk loci in Swedish and Indian women.

**Conclusions**: GDM is more common in Indian than in Swedish women, which partially can be attributed to differences in insulin secretion. There was marked heterogeneity in the association of genetic variants with GDM in the two populations.

## Introduction

Gestational diabetes mellitus (GDM) is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy" [1, 2]. GDM develops when women no longer can increase their insulin secretion to meet the increased demands of insulin resistance during the third trimester [3, 4]. [3]. The risk of GDM is exacerbated by age, obesity, and a family history of GDM and T2D [5, 6]; however, the exact etiology is unknown. GDM patients are at increased risk of gestational hypertension, pre-eclampsia during pregnancy, and type 2 diabetes (T2D), as well as metabolic syndromes later in life [7]. Untreated GDM predisposes to adverse neonatal outcome and predicts later development of T2D in both the mothers and offspring [8].

Ethnicity has a great impact on the prevalence of GDM and the prevalence of GDM differs between 1% and 10-35% in different populations [9-11]. Individuals of Asian descents have 2-7-fold greater risk of developing GDM than their Caucasian counterparts [12, 13]. These differences can have several explanations including differences in predisposing risk factors [9] but also different screening and diagnostic criteria applied [14, 15].

There is no international consensus on diagnostic criteria, which hampers the understanding and clinical care of GDM patients [16]. In southern Sweden the diagnosis of GDM is defined using the EASD (European Association for the Study in Diabetes) criteria based on a 75-g oral glucose tolerance test (OGTT). [17]. A 2-h capillary glucose concentration of 9 mmol/l (or 10 mmol/l plasma) or higher is regarded as diagnostic for GDM, [18]. Based on these criteria, the prevalence of GDM in Sweden was estimated to be 2.6% in a study published 2012 [11]. In India, various diagnostic criteria have been employed including the IADPSG (International Association of the Diabetes and Pregnancy Study Groups), the ADA (American Diabetes Association) and the WHO

(World Health Organization) 1999 or 2013 criteria [19, 20]. The IADPSG and WHO2013 criteria were proposed based on findings from the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study, which showed a continuous and graded relationship between maternal glycemia and adverse fetal outcomes [21]. On the other hand, the WHO1999 criteria are based on cut-off values for diabetes and impaired glucose tolerance outside pregnancy [22, 23]. Prevalence of GDM in the North Indian Punjabi population was 35% using the WHO2013 criteria but only 9% the using WHO1999 criteria [10]. While these criteria can influence estimates of insulin secretion and sensitivity differently, previous data suggest that Indian GDM women are very insulin resistant but it is not known how differences in insulin secretion or action contribute to the different prevalences of GDM between India and Europe.

A family history of T2D or GDM increases risk of GDM, suggesting a genetic component. Several candidate gene studies have confirmed a role for T2D risk loci in GDM. To our knowledge, only one GWAS study on GDM in Korean women has been published [24-26]. Few studies have examined the genetic susceptibility to GDM in the Indian population including 2 studies based on South Indian women reported the association of variants in CDKAL1, HMG20A and HNF4A with GDM [27, 28]. It is quite possible that the genetic background contributing to GDM differs between women of North Indian and of Scandinavian origin and could explain some also cause disparities in the prevalence of GDM. To address these questions, we examined phenotypic and genetic differences in pregnant women with GDM from India and Sweden.

## Methods

### Study population and GDM diagnosis

## Swedish Cohorts

**Malmö Study:** From a total of 188 women with GDM referred to the Department of Endocrinology

in Malmö, between 1995 and 1999, 83 women of Swedish ethnicity were included in the present study. The diagnosis of GDM was in all women based on 2-h capillary blood glucose measurementof $\geq$ 9.0 mmol/l (corresponding to a plasma glucose value of $\geq$ 10 mmol/l) during a universally applied 75-g OGTT at 27-28 weeks of gestation. The OGTT was then repeated with venous measurements of blood glucose 0, 30, 60 and 120 min with simultaneous measurements of insulin (mU/l). Blood glucose values were converted to plasma glucose by multiplying by a factor of 1.11 according to the IFCC recommendation [18].

**Mamma study:** Pregnant women giving birth in the County of Skåne in southern Sweden between 2003 and 2005 were recruited to the Mamma study. A 75-g OGTT was offered to all women at 27-28 week of gestation in routine antenatal care. From a total of 424 women of Swedish ancestry, 89 women with GDM (2-h capillary plasma glucose concentration $\geq$ 10.0mmol/l), and 335 women without GDM (2-h capillary glucose concentration < 9.9 mmol/l) with DNA available were included in the study.

Informed consent was obtained from all participants and the study approved by the Ethics Committee of Lund's University. Glucose concentrations were measured using HemoCue devices (HemoCue, Ängelholm, Sweden). Serum insulin concentrations were measured with an enzyme-linked immunosorbent assay (ELISA, Dako, Glostrup, Denmark), and homeostasis model assessment calculation (HOMA2-B and HOMA2-IR) calculated for estimation of insulin secretion and action, using the HOMA2 calculator v2.2.3 (http://www.dtu.ox.ac.uk/homacalculator/) [29].

## Indian cohort

**Punjabi GDM study:** A multistage protocol was applied for recruiting study subjects between 2009 and 2012 in a representative group of 5100 pregnant women from Punjab. All women

between gestational weeks 24-28 weeks visiting selected study sites, both urban and rural for antenatal checkup were screened. Information of demographic factors including diet, age, family history of diabetes, BMI, habitat (urban / rural), education status and religion was obtained in a standard Questionnaire by trained health care professional. Written material in 3 languages (Hindi, English and Punjabi and verbal training sessions were provided to the women) before giving informed consent to the study, which was approved by the local Ethics Committee. All participants underwent an OGTT with serum sample drawn at time 0 min for glucose and insulin and glucose measured at 120 min as capillary glucose [10]. Based on availability of DNA and clinical data a total of 4018 women were included in the study. **Since only 2-h glucose values were available in the Malmö study, GDM here was defined as 2-h glucose ≥10 mmol /l.**

## Genotyping

DNA was extracted from buffy coats using the Q1AGEN Autopure W kit. Six SNPs previously associated with GDM and /or T2D in Indian people [27, 28, 30-32] (P4 supplementary table 1) and 79 SNPs associated with T2D/GDM in other populations [33] were genotyped in the current study using a Sequenom mass ARRAY platform or Taqman. All SNPs passed the Bonferroni threshold of < 0.0006 for Hardy-Weinberg equilibrium test.

## Statistical analyses

Anthropomorphic and glycemic measures are presented as means ± SEM. Significance of differences between group means was tested by the Mann-Whitney U test or analysis of variance or covariance (ANCOVA) with BMI and age as covariates. Inverse normal transformation was used to normalize data with skewed distributions.

Allele and genotype frequencies were compared between groups by chi-square or Fisher's exact test. Association of selected SNPs with GDM was assessed by logistic regression analysis adjusted for maternal age and results presented as ORs with their 95% confidence intervals (CI) in plink

(plink v1.09). Alleles were also analyzed for association with glucose, insulin and HOMA2-B and HOMA2-IR) using linear regression model adjusted for age.

Two-sided p values of less than 0.05 were considered statistically significant. For the Indian study population, power to detect association with GDM (125 cases and 3893 controls) for 79 markers at a significance level of 0.05, was 0.04 under the additive model and 0.12 under the multiplicative model. at 0.50 MAF and OR of 1.5. For the Swedish cohort with at 245 cases and 335 controls, the corresponding figures were 0.06 and 0.17 respectively. For association with quantitative traits, power to detect an association was 1 at alpha 0.05 for an allele frequency of 0.3 [34, 35]. Polygenic risk scores which is the sum of trait-associated alleles across many genetic loci, typically weighted by effect sizes were calculated using PRsice [36]. Polygenic risk scores (PRS) were created from previous GWAS SNPs for T2D to assess the genetic overlap between T2D and GDM. 12 SNPs previously associated with insulin secretion indices and 5 SNPs with insulin resistance were here used to construct genetic risk scores (GRR) for insulin secretion and action respectively using PLINK [37].

## Results

### Clinical characteristics

Applying Swedish GDM criteria cut-offs, the prevalence of GDM in the Punjabi population was 3.11% (125 out of 4018 women). Swedish women with GDM were >10 years older ($p= 1.21x10^{-40}$) and had higher BMI ($28.09 \pm 0.64$ vs $24.08 \pm 0.42$, $p = 3.76 x10^{-07}$) than the e Punjabi women (table 1).

The India GDM women had higher fasting and 2 hour glucose associated with lower fasting insulin and HOMA2-B (76.6±3.83 vs 123.98±7.54, p=2.99x10-9) as well as better insulin sensitivity

estimated as HOMA2-IR (1.036±0.97 vs 1.26±0.097, *p*=0.001) compared with Swedish GDM women adjusted for BMI and age (table 1).

## Association of genetic loci with GDM in Indian and Swedish women

**SNPs previously associated with GDM/T2D in India** (P4 supplementary table 1, 3). The risk allele C of rs7178572 SNP near *HMG20A* was nominally associated with risk of GDM in Indian but not in Swedish women (p =0.03, Table 2,), thereby replication previous findings in Indian populations. rs7178572 is an eQTL for *PSTPIP1* (p = 0.003) and *HMG20A* (p=0.007) genes in human pancreatic islets (P4 supplementary table 7).

The Asp/Tyr missense variant of SNP rs1799999 in the *PP1RR3A* gene, which previously has been shown to associate with T2D risk in Jat Sikhs, showed a trend towards significance in Indian (p = 0.06) but not Swedish women (p =0.5) (table 2). The variant was also nominally associated with decreased 2-hour insulin in Swedish women (p = 0.02, supplementary table 6).

**SNPs previously associated with GDM or T2D in Europeans:** Of 4 SNPs previously associated with Scandinavian GDM [24, 25] study populations (P4 supplementary table 2), the rs1111875 SNP near the *HHEX*/*IDE* genes was nominally associated with GDM in Swedish women (p = 0.031, table 2). rs1111875 variants influences expression of *NHP2P1* and *BTAF1* genes in human pancreatic islets (P4 supplementary table 7). rs1111875 differed in frequency between Indian and Swedish women (p = <0.0001, table 3, fig 3).

The risk allele of rs11708067 was also associated with increased 2-hour glucose (p= 0.037), decreased HOMA2-B (p = 0.010) in Swedish GDM women (P4 supplementary table 4). The same SNP was associated with 2 hour glucose in all Swedish women (GDM+non-GDM) (β = 0.12 ± 0.04, p=0.004) (P4 supplementary table 4).

The rs11605924 SNP in the intron of the *CRY2* gene was nominally associated with GDM in both study populations. Interestingly, the T2D risk allele A was protective in the Indian population (OR = 0.67, p = 0.0026, P4 supplementary table 5) whereas associated with risk in the Swedish women (OR = 1.44, p=0.012, P4 supplementary table 5). The same SNP showed differences in frequencies between Indian and Swedish women (p = <0.0001 and 0.0004) respectively (table 3, fig 3). rs11605924 nominally influenced expression of CRY2 in human pancreatic islets (P4 supplementary table 7).

The rs8090011 SNP in intron of the *LAMA1* gene was nominally associated with GDM risk in Swedish women. The same SNP also associated with decreased 2-hour insulin concentration (P4 supplementary table 6).

SNPs rs12571751 in the intron of *ZMIZ1*, rs5945326 near *DUSP9*, and rs2237895 in the intron of *KCNQ1* were nominally associated with GDM in Swedish women whereas only the rs7593730 SNP near *RBMS1* was associated with GDM risk in Indian women.

Genetic risk scores (GRR) based on T2D / GDM loci predicted GDM risk in Indian (Fig 2A) but not Swedish women (Fig 2B). GRR for insulin resistance was 0.91 (±1.2, p = 0.064) for Swedish whereas 0.04 (±1.2, p = 0.25) for Indian women. GRR for insulin secretion was -0.08 (±0.043, p = 0.46) for Swedish and -0.008 (±0.037, p = 0.83) for Indian women.

Additionally, significant differences in frequency of GDM risk alleles in rs560887 in *G6PC2* (p = 0.0008), rs11708067 in *ADCY5* (p = 0.005), rs10010131 in *WFS1* (p = <0.0001) and rs10811661 (p=0.0073) in *CDKN2B* between Indian and Swedish women with GDM were seen (table 3, fig 3).

## Discussion

Key findings in the current study was that Indian and Swedish women with GDM showed clear

differences in insulin secretion and action, which not fully could be accounted for by genetic effects. Despite being on average 10 years younger, North Indian women had a higher prevalence (3.11%) of GDM than previously reported in Swedish women (2.4%) from comparable time periods [11]. To note, the prevalence figure 2.4 during 2009-2012 was based on a study population of mixed ethnicity residing in Sweden, and a lower prevalence could be expected if only based on Swedish women (estimated 1.2-1.5%) [38]. This is consistent with previous reports showing higher GDM frequency in populations with a high frequency of T2D [39]. The prevalence of T2D was slightly higher in India than in Sweden (8.8% vs 6.8%) [40, 41].

Indian women had lower HOMA2-B, which was associated with lower BMI and better insulin sensitivity than Swedish older GDM women [42]. The better insulin sensitivity could be a corollary of the lower BMI (Figure 1).

As Indian women seem to develop GDM at lower BMI and with better insulin sensitivity, this could point at a more severe defect in insulin secretion, which also was supported by lower HOMA2-B. We though need to acknowledge that HOMAs are only surrogate markers for insulin secretion and action.

Previously, 6 loci have been associated with T2D or GDM in India [27, 28, 30-32]. Of them, the rs7178572 SNP near the *HMG20A* gene was associated with GDM in Indian but not in Swedish women. This SNP has though been associated with T2D in European populations [43]. Notably, it was only when we used the older WHO1999 criteria with higher cut-off values fro glucose we could observe this association. Earlier studies have shown a weak association of rs7178572 with *PSTPIP1* gene expression in lymphoblastoid cell lines [43]. Here we showed that this SNP also was an eQTL in human pancreatic islets influencing expression of both *PSTPIP1* and *HMG20A*.

The Proline-Serine-Threonine Phosphatase Interacting Protein 1 (*PSTPIP1)* gene is a tyrosine phosphatase that inhibits T-cell activation upon T-cell receptor (TCR) and *CD28* engagement, regardless of CD2 co-stimulation [44]. The *HMG20A* gene had higher expression in islets than in muscle and adipose tissue [45] and a transient increase in expression levels were observed upon glucose stimulation [45]. *HMG20A* has been reported to be down-regulated in T2D and T1D islets, and knockdown of *HMG20A* decreased expression of *NEUROD*, *INS* and *GK* with an accompanying impairment in GSIS [45]. Therefore, this SNP could through its eQTL effect on HMG20A expression in islets be a plausible candidate gene for GDM.

The early GWAS SNP rs1111875 near the *HHEX/IDE* genes was associated with GDM risk in Swedish women but not Indian. Notably, the T2D risk SNP rs11605924 in *CRY2* showed a protective effect against GDM in Indian but conferred risk in Swedish women. *CRY2* encodes the circadian rhythm gene cryptochrome 2, and is a target for the *CLOCK-BMAL1*, which are core components of the endogeneous clock. The *CRY2* variant is also associated with fasting glucose and reduced liver fat content in human liver [46]. CRY2 mRNA expression has been associated with hepatic triglyceride content [46] suggesting that *CRY2* could serve as a switch between fat and glucose metabolism in the liver [46]. Interestingly, as the same allele had effects in opposite directions in Indian and Swedish populations, the question rises whether risk seen in the Swedish population could be related to marked differences in circadian rhythm during seasons in Sweden, which is lacking in India.

Interestingly, significant frequency differences were observed for 6 out of 12 GDM risk alleles, of which two showed a reversal of major and minor alleles. A previous study identified 12 T2D risk alleles in 5 or more populations shared a consistent pattern of statistically significant decreasing frequencies from Africa through Europe to East Asia. These decreasing frequencies further caused

significant differentiation of genetic risk of T2D with higher risk in the African and lower in the Asian populations. The authors hypothesized that these differences might be caused by the promotion of energy storage and environments appropriate usage and inconsistent energy intake [47]. *CRY2* could potentially represent such an example and further studies will be needed to dissect the mechanisms.

Different criteria for GDM are based upon different risks. WHO1999 clearly identifies a more severe dysregulation of glucose metabolism than the other criteria. On the other hand, WHO 2012 is supposed to identify risk of malformations in the offspring. The PRS derived from T2D loci identified a shared genetic background between GDM and T2D in India, whereas power in Sweden was too low. This does not exclude the possibility that a GWAS could identify shared genetic background also for the other criteria and thereby risk for offspring.

Taken together Indian women develop GDM at lower BMI and better insulin sensitivity than Swedish women pointing at problems to increase insulin secretion to meet the increased demands imposed by even small increases in insulin resistance during the third trimester. The genetic contribution seems to be shared with T2D.

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| Variable | Swedish | N (Swedish) | Indian | N (Indian) | P value |
|---|---|---|---|---|---|
| Age | 31.78 ± 0.36 | 149 | 20.97 ± 0.33 | 125 | $1.21x10^{-40}$ |
| BMI | 28.09 ± 0.64 | 56 | 24.08 ± 0.42 | 125 | $3.76 x10^{-07}$ |
| Fasting glucose[a] | 4.79 ± 0.10 | 49 | 5.72 ± 0.15 | 125 | $1.60 x10^{-05}$ |
| 2 hour glucose[a] | 10.99 ± 0.08 | 149 | 12.07 ± 0.20 | 125 | $3.13 x10^{-02}$ |
| Fasting insulin[a] | 78.17 ± 12.67 | 51 | 51.8 ± 5.35 | 125 | $3.74 x10^{-06}$ |
| HOMA2-B[a] | 123.99 ± 7.55 | 45 | 76.61 ± 3.83 | 109 | $3.00 x10^{-09}$ |
| HOMA2-IR[a] | 1.26 ± 0.10 | 45 | 1.04 ± 0.10 | 109 | $1.11 x10^{-03}$ |

**Table 1. Clinical characteristics of Indian and Swedish women with GDM (diagnosed based on 2 hour glucose cut-offs >=10mmol/l). Mean ± SEM are represented. P-values are calculated based on inverse normal transformed data.**

[a] *adjusted for age and BMI*

| | | | | | | INDIA | | | SWEDEN | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **CHR** | **SNP** | **BP** | **Gene** | **Location** | **A1** | **n** | **OR (CI)** | **P** | **n** | **OR (CI)** | **P** |
| 15 | rs7178572 | 77454848 | *HMG20A/DUSP9* | intergenic | T | 3346 | 0.75 (0.57 – 0.98) | **0.03** | 476 | 0.8253 (0.59 – 1.15) | 0.25 |
| 10 | rs1111875 | 92703125 | *HHEX/IDE* | intergenic | G | 3675 | 1.02 (0.79 - 1.32) | 0.86 | 443 | 0.71 (0.52 - 0.97) | **0.031** |
| 3 | rs11708067 | 123346931 | *ADCY5* | intron | G | 3648 | 1.29 (0.97 - 1.71) | 0.084 | 466 | 0.69 (0.48 -1.00) | 0.054 |
| 11 | rs11605924 | 45851540 | *CRY2* | intron | A | 3679 | 0.67 (0.52 - 0.87) | **0.0026** | 484 | 1.44 (1.08-1.91) | **0.0129** |
| 10 | rs12571751 | 79182874 | *ZMIZ1* | intron | G | 3390 | 1.24 (0.95 - 1.61) | 0.11 | 492 | 1.39 (1.05-1.83) | **0.021** |
| 11 | rs2237895 | 2835964 | *KCNQ1* | intron | C | 3463 | 0.81 (0.62 - 1.06) | 0.13 | 410 | 1.43 (1.06-1.94) | **0.0204** |
| 2 | rs243088 | 60341610 | *BCL11A* | intergenic | T | 3497 | 1.29 (0.99 - 1.68) | 0.06 | 425 | 1.13 (0.83-1.55) | 0.41 |
| X | rs5945326 | 153634467 | *DUSP9* | intergenic | G | 3377 | 1.15 (0.88 - 1.50) | 0.29 | 495 | 0.69 (0.49-0.98) | **0.035** |
| 15 | rs7177055 | 77540420 | *HMG20A* | intergenic | G | 3680 | 0.74 (0.57 - 0.96) | **0.024** | 457 | 0.91 (0.65-1.27) | 0.58 |
| 2 | rs7593730 | 160314943 | *RBMS1/ITGB6* | intronic | T | 3673 | 0.87 (0.63 - 1.21) | **0.40** | 457 | 0.97 (0.68-1.37) | 0.86 |
| 18 | rs8090011 | 7068463 | *LAMA1* | intron | G | 3683 | 1.02 (0.79 - 1.32) | 0.89 | 457 | 1.49 (1.11-2.01) | **0.0090** |

**Table 2. Association of previously reported GDM and T2D with risk of GDM in Indian and Swedish women. OR = odds ratio, CI = confidence intervals. P = p-value.**

| | | India | | | | | | Sweden | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CHR | SNP | minor/major | N | minor_n | MAF | major_n | MajAF | minor/major | N | minor_n | MAF | major_n | MajAF | p |
| 2 | rs560887 | A/G | 244 | 32 | 0.1311 | 212 | 0.8689 | A/G | 192 | 50 | 0.2604 | 142 | 0.7396 | **0.0008** |
| 3 | rs11708067 | G/A | 246 | 67 | 0.2724 | 179 | 0.7276 | G/A | 256 | 43 | 0.168 | 213 | 0.832 | **0.005** |
| 3 | rs4402960 | T/G | 242 | 93 | 0.3843 | 149 | 0.6157 | T/G | 176 | 56 | 0.3182 | 120 | 0.6818 | 0.1794 |
| 4 | rs10010131 | A/G | 242 | 62 | 0.2562 | 180 | 0.7438 | A/G | 224 | 100 | 0.4464 | 124 | 0.5536 | **<0.0001** |
| 6 | rs7754840 | C/G | 232 | 73 | 0.3147 | 159 | 0.6853 | C/G | 232 | 79 | 0.3405 | 153 | 0.6595 | 0.621 |
| 6 | rs7756992 | G/A | 230 | 70 | 0.3043 | 160 | 0.6957 | G/A | 234 | 70 | 0.2991 | 164 | 0.7009 | 0.9197 |
| 8 | rs13266634 | T/C | 244 | 56 | 0.2295 | 188 | 0.7705 | T/C | 260 | 69 | 0.2654 | 191 | 0.7346 | 0.3555 |
| 9 | rs10811661 | C/T | 244 | 32 | 0.1311 | 212 | 0.8689 | C/T | 224 | 26 | 0.1161 | 198 | 0.8839 | **0.0073** |
| 9 | rs2796441 | T/C | 244 | 106 | 0.4344 | 138 | 0.5656 | T/C | 252 | 106 | 0.4206 | 146 | 0.5794 | 0.7857 |
| 10 | rs1111875* | G/A | 240 | 107 | 0.4458 | 133 | 0.5542 | A/G | 242 | 85 | 0.3512 | 157 | 0.6488 | **<0.0001** |
| 11 | rs5219 | T/C | 234 | 92 | 0.3932 | 142 | 0.6068 | T/C | 126 | 58 | 0.4603 | 68 | 0.5397 | 0.2203 |
| 11 | rs11605924* | A/C | 240 | 94 | 0.3917 | 146 | 0.6083 | C/A | 270 | 121 | 0.4481 | 149 | 0.5519 | **0.0004** |

**Minor and major alleles are reversed*

**Table 3. Allele frequency comparison of previously reported GDM loci in Indian and Swedish women with GDM (Swedish diagnosis criteria). N =total number of alleles, minor_n = total number of minor alleles, MAF = minor allele frequency, MajAF = major allele frequency, p = p-value for the frequency differences between India and Sweden.**

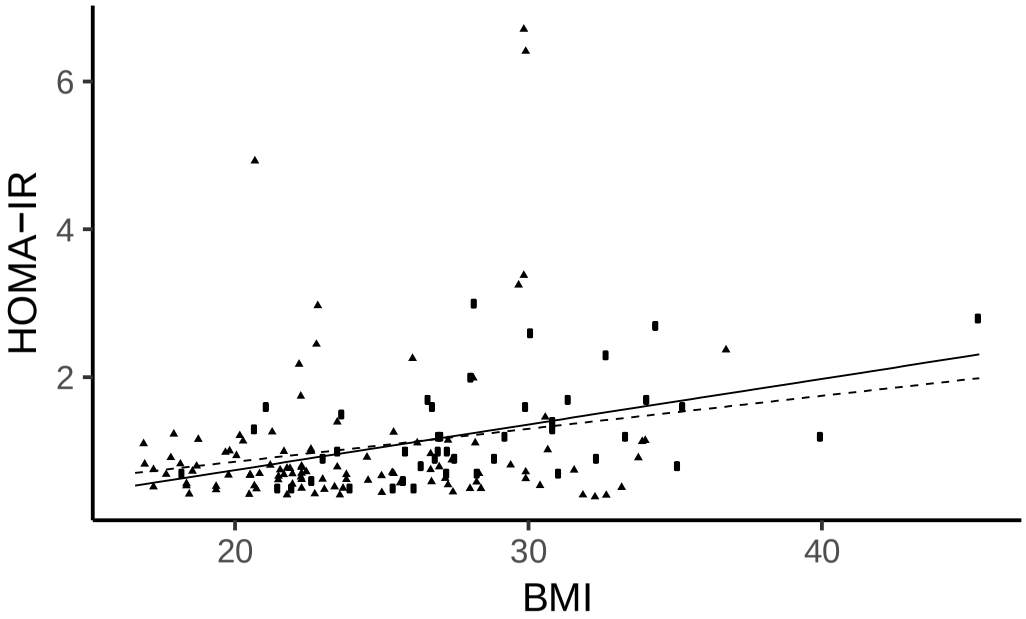


**Figure. 1. Relationship between HOMA-IR and BMI in Indian (solid triangles and dashed line line) and Swedish (empty circles and solid line) women with GDM**

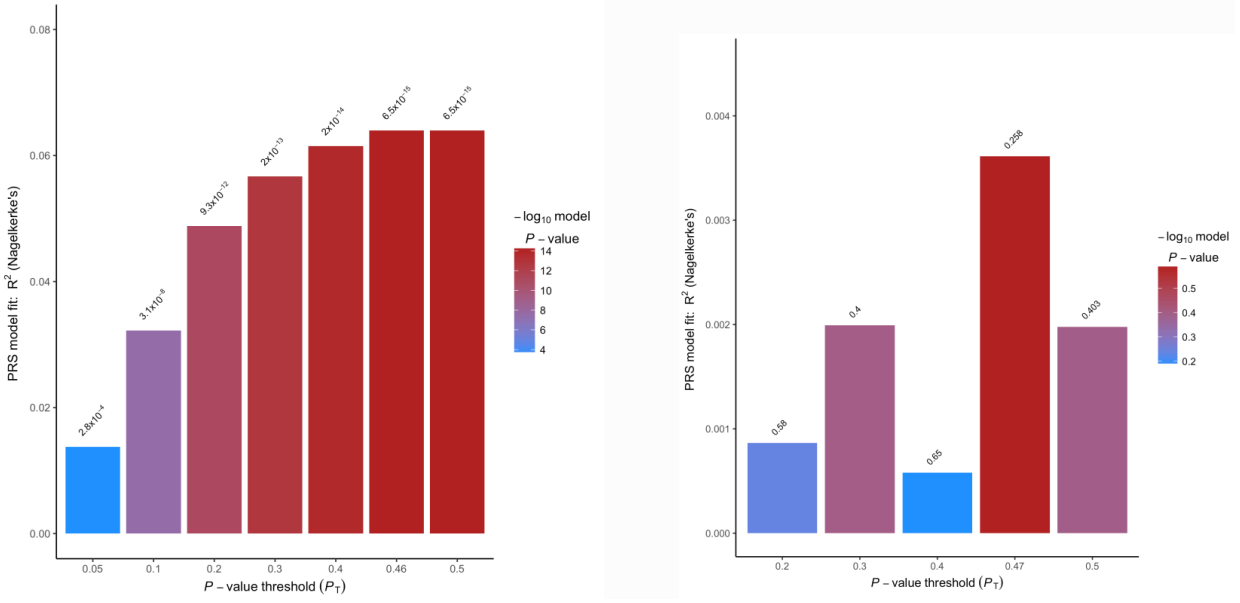


**Figure 2. Bar plot from PRSice showing results at broad *P*-value thresholds for T2D polygenic risk scores predicting GDM in (A) Indian And (B) Swedish women. (A) is indicative of a role of common T2D genetic risk variants in GDM etiology in the Indian population.**

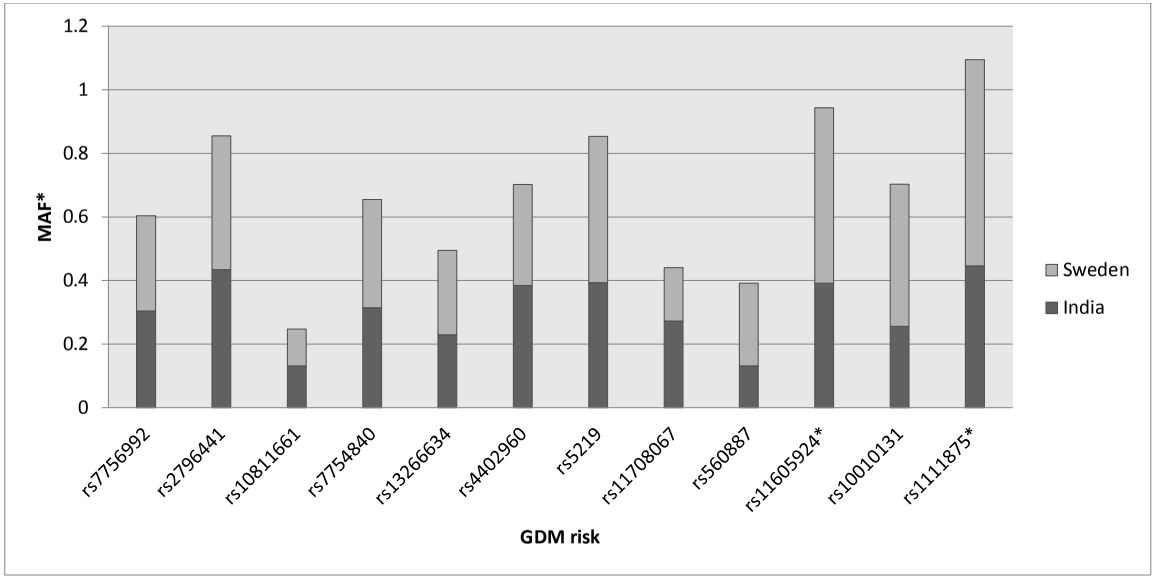


**Figure 3. Frequencies of minor alleles (as defined in EUR population) of previously reported GDM loci in Indian and Swedish women with GDM. Rs11605924 and rs 1111875 showed an interchange of major and minor alleles in Indian GDM women.**

**P4 Supplementary table 1. 6 T2D/GDM associated SNPs selected from previously studies based on Indian population**

| SNPs | GENE / nearest Gene | location | Chr | locus | RA | OA | RAF | Trait | References |
|---|---|---|---|---|---|---|---|---|---|
| rs1799999 | PP1G.G | Missense coding | 7 | 7q31.1 | C | A | 1.6 | T2D | Sokhi et al Mol Genet Genomics 2015 |
| rs4812829 | HNF4A | intronic | 20 | 20q13.12 | G | A | 1.64 | GDM | Kanthimathi, Molecular Genetics and Genomics, 2017 |
| rs689 | INS | Intronic / 5'UTR | 11 | 11p15.5 | A | T | 3.1 | T2D | Sokhi et al Mol Genet Genomics 2015 |
| rs7178572 | HMG20A | intronic | 15 | 15q24.3 | C | T | 1.5 | GDM | Kanthimathi, Molecular Genetics and Genomics, 2017 |
| rs9552911 | SGCG | intronic | 13 | 13q12.12 | A | G | 0.67 | T2D | Saxena, Diabetes, 2013 |
| rs998451 | TMEM163, RAB3GAP1 | intronic | 2 | 2q21.3 | G | A | 1.61 | T2D | Tabassum et al, Diabetes 2013 |

P4 **Supplementary table 2. T2D associated SNPs selected from previously published GWAS studies upto 2012 and GDM associated loci (*) from previous candidate and GWAS studies.**

| SNPs | GENE / nearest Gene | location | Chr | locus | RA | OA | RAF | Trait | References |
|---|---|---|---|---|---|---|---|---|---|
| rs10923931 | NOTCH2 | intron | 1 | 1p12 | T | G | 0.10 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs2296172 | MACF1 | coding - missense | 1 | 1p34.3 | G | A | | T2D | A. Albrechtsen et al, Diabetologia, 2013 |
| rs340874 | PROX1 | intergenic | 1 | 1q41 | C | T | 0.45 | Fasting glucose / insulin secretion / T2D | Dupuis et al Nat Genet 2010 |
| rs243021 | BCL11A | intergenic | 2 | 2p16.1 | A | G | 0.46 | T2D | Voight et al DIAGRAM 2010 |
| rs243088* | BCL11A | intergenic | 2 | 2p16.1 | T | A | 0.45 | T2D / GDM | Morris, naturegenetics 2012 |
| rs7578597 | THADA | coding - missense | 2 | 2p21 | T | C | 0.90 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs3923113 | GRB14 | intergenic | 2 | 2q24.3 | A | C | 0.64 (0.74) | T2D | Kooner natgen 2012; Morris natgen, 2012 |
| rs13389219 | GRB14 | intergenic | 2 | 2q24.3 | C | T | 0.60 | T2D | Morris, naturegenetics 2012 |
| rs7607980 | COBL1 | coding - missense | 2 | 2q24.3 | C | T | | T2D | A. Albrechtsen et al, Diabetologia, 2013 |
| rs560887 | G6PC2/ABCB11 | intron | 2 | 2q31.1 | C | T | 0.67 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs7578326 | KIAA1486/IRS1 | intron of uncharacterized LOC646736 | 2 | 2q36.3 | A | G | 0.64 | T2D | Voight et al DIAGRAM2 2010 |
| rs2943641 | IRS1 | intergenic | 2 | 2q36.3 | C | T | 0.63 | Fasting insulin /T2D / insulin sensitivity | Rung et al. Nat Genet 2010 |
| rs4675095 | IRS1 | intron | 2 | 2q36.3 | A | T | 0.94 | fasting glucose/ insulin sensitivity | Dupuis et al Nat Genet 2010 |
| rs7593730* | RBMS1/ITGB6 | intronic | 2 | 9q24.2 | T | C | 0.23 | T2D / GDM | Qi et al. Hum Molec Gen. 2010 |
| rs4607103 | ADAMTS9-AS2 | intron | 3 | 3p14.1 | C | T | 0.76 | T2D / GDM | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs831571 | PSMD6 | intergenic | 3 | 3p14.1 | C | T | 1 (0.688) | Asian T2D | Cho natgen 2012 |
| rs1801282 | PPARG | coding - missense | 3 | 3p25.2 | C | G | 0.86 | T2D / Insulin sensitivity | DGI, MIT and LU, Science 2007 |
| rs11708067* | ADCY5 | intron | 3 | 3q21.1 | A | G | 0.77 | T2D / 2hr glucose / Fasting Glucose / HOMA B / GDM | Saxena et al. Nat Genet 2010 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| rs11920090 | SLC2A2 | intron | 3 | 3q26.2 | T | A | 0.86 | Fasting glucose / HOMA B | Dupuis et al Nat Genet 2010 |
| rs4402960 | IGF2BP2 | intron | 3 | 3q27.2 | T | G | 0.29 | T2D | DGI, MIT and LU, Science 2007 |
| rs10010131 | WFS1 | intron | 4 | 4p16.1 | G | A | 0.60 | T2D | Sandhu et al nature genetics 2007, Lyssenko et al, NEJM 2008 |
| rs6815464 | MAEA | intron | 4 | 4p16.3 | C | G | 0.522 - 0.64 | Asian T2D | Cho natgen 2012 |
| rs459193 | ANKRD55 | intergenic | 5 | 5q11.2 | G | A | 0.70 | T2D | Morris, naturegenetics 2012 |
| rs4457053 | ZBED3 | intron of ZBED3-AS1 | 5 | 5q13.3 | G | A | 0.26 | T2D | Voight et al DIAGRAM2 2010 |
| rs9470794 | ZFAND3 | intron | 6 | 6p21.2 | C | T | 0.50 (0.20) | Asian T2D | Cho natgen 2012 |
| rs7754840 | CDKAL1 | intron | 6 | 6p22.3 | C | G | 0.30 | T2D | Steinthorsdottir, Nat Gen 2007, DGI, MIT and LU, Science 2007 |
| rs7756992 | CDKAL1 | intron | 6 | 6p22.3 | G | A | 0.25 | T2D | Steinthorsdottir, Nat Gen 2007 |
| rs4607517 | GCK | intergenic | 7 | 7p13 | A | G | 0.20 | Fasting glucose/T2D / insulin sensitivity / HOMA B | Dupuis et al Nat Genet 2010 |
| rs864745 | JAZF1 | intron | 7 | 7p15.1 | T | C | 0.50 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs2191349 | DGKB/TMEM195 | intergenic | 7 | 7p21.2 | T | G | 0.50 | Fasting glucose / T2D / Insulin secretion | Dupuis et al Nat Genet 2010 |
| rs17168486 | DGKB | intergenic | 7 | 7p21.2 | T | C | 0.19 | T2D | Morris, naturegenetics 2012 |
| rs6467136 | GCC1-PAX4 | intergenic | 7 | 7q32.1 | G | A | 0.50 (0.81) | Asian T2D | Cho natgen 2012 |
| rs516946 | ANK1 | intron | 8 | 8p11.21 | C | T | 0.76 | T2D | Morris, naturegenetics 2012 |
| rs896854 | TP53INP1 | intron | 8 | 8q22.1 | T | C | 0.48 | T2D | Voight et al DIAGRAM2 2010 |
| rs13266634 | SLC30A8 | coding - missense | 8 | 8q24.11 | C | T | 0.70 | T2D | Sladek R Nature 2007 |
| rs10811661 | CDKN2B | intergenic | 9 | 9p21.3 | T | C | 0.80 | T2D | DGI, MIT and LU, Science 2007, Gupta, Diabetologia 2012, Wu Y, Diabetes 2008 |
| rs13292136 | TLE4 (CHCHD9) | intergenic | 9 | 9q21.31 | C | T | 0.93 | T2D | Voight et al DIAGRAM2 2010 |
| rs2796441 | TLE1 | intergenic | 9 | 9q21.32 | G | A | 0.57 | T2D | Morris, naturegenetics 2012 |
| rs7034200 | GLIS3 | intron | 9 | 9q24.2 | A | C | 0.50 | Fasting glucose /T2D/proinsulin to insulin / insulin secretion | Dupuis et al Nat Genet 2010 |
| rs12779790 | CDC123,CAMK1D | intergenic | 10 | 10p13 | G | A | 0.18 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs12571751* | ZMIZ1 | intron | 10 | 10q22.3 | A | G | 0.52 | T2D / GDM | Morris, naturegenetics 2012 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| rs1111875* | HHEX/IDE | intergenic | 10 | 10q23.33 | C | T | 0.52 | T2D / GDM | DGI, MIT and LU, Science 2007 |
| rs7903146 | TCF7L2 | intronic / promoter | 10 | 10q25.2 | T | C | 0.50 | T2D | Grant SFA, Nat genetics 2006, |
| rs553668 | ADRA2A | UTR-3 | 10 | 10q25.2 | A | G | 0.50 | T2D | Rosengren Science 2009 |
| rs10885122 | ADRA2A | intergenic | 10 | 10q25.2 | G | T | 0.90 | Fasting glucose / T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs7944584 | MADD | intron | 11 | 11p11.2 | A | T | 0.75 | Fasting proinsulin / T2D / Fasting glucose / HOMA B | Dupuis et al Nat Genet 2010 |
| rs5219 | KCNJ11 | coding - missense | 11 | 11p15.1 | T | C | 0.46 | T2D | DGI, MIT and LU, Science 2007 |
| rs2237895* | KCNQ1 | intron | 11 | 11p15.4 | C | T | 0.33 | T2D / GDM | Yasuda natgen 2008 |
| rs163184 | KCNQ1 | intron | 11 | 11p15.4 | G | T | 0.51 | T2D | Yasuda natgen 2008; Morris natgen, 2012 |
| rs2237892 | KCNQ1 | intron | 11 | 11p15.4 | C | T | 0.69 | T2D | Yasuda Natgen 2008 |
| rs231362 | KCNQ1 | intron | 11 | 11p15.5 | G | A | 0.52 | Fasting glucose / T2D | Voight et al DIAGRAM2 2010 |
| rs174550 | FADS1 | intron | 11 | 11q12.2 | T | C | 0.63 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs1552224 | CENTD2 | intergenic | 11 | 11q13.4 | A | C | 0.88 | T2D | Voight et al DIAGRAM2 2010 |
| rs10830963 | MTNR1B | intron | 11 | 11q14.3 | G | C | 0.30 | T2D / Fasting glucose / HOMA B | Prokopenko natgen 2008 |
| rs10842994 | KLHDC5 | intergenic | 12 | 12p11.22 | C | T | 0.80 | T2D | Morris, naturegenetics 2012 |
| rs11063069 | CCND2 | intergenic | 12 | 12p13.32 | G | A | 0.21 | T2D | Morris, naturegenetics 2012 |
| rs1153188 | DCD | intergenic | 12 | 12q13.2 | A | T | 0.73 | T2D | Zeggini et al Nat Gen 2009 |
| rs1531343 | HMGA2 | intron of pseudogene | 12 | 12q14.3 | C | G | 0.10 | T2D | Voight et al DIAGRAM2 2010 |
| rs7961581 | TSPAN8,LGR5 | intergenic | 12 | 12q21.1 | C | T | 0.27 | T2D | Zeggini, natgen, 2008, Lyssenko et al, NEJM 2008 |
| rs35767 | IGF1 | nearGene-5 | 12 | 12q23.2 | G | A | 0.88 | Fasting glucose/Fasting insulin/T2D / Insulin sensitivity | Dupuis et al Nat Genet 2010 |
| rs7957197 | OASL/TCF1/HNF1A | intron of OASL | 12 | 12q24.31 | T | A | 0.85 | T2D | Voight et al DIAGRAM2 2010 |
| rs11071657 | FAM148B | intergenic | 15 | 15q22.2 | A | G | 0.77 | Fasting glucose /T2D / HOMA B | Dupuis et al Nat Genet 2010 |
| rs17271305 | VPS13C | intron | 15 | 15q22.2 | G | A | 0.42 | 2hr glucose | Saxena et al. Nat Genet 2010 |
| rs7177055* | HMG20A | intergenic | 15 | 15q24.3 | A | G | 0.68 | T2D / GDM | Morris, naturegenetics 2012 |
| rs11634397 | ZFAND6 | intergenic | 15 | 15q25.1 | G | A | 0.60 | T2D | Voight et al DIAGRAM2 2010 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| rs8042680 | PRC1 | intron | 15 | 15q26.1 | A | C | 0.22 | T2D | Voight et al DIAGRAM2 2010 |
| rs7202877 | BCAR1 | intergenic | 16 | 16q23.1 | T | G | 0.89 | T2D | Morris, naturegenetics 2012 |
| rs8090011* | LAMA1 | intron | 18 | 18p11.31 | G | C | 0.36 | T2D / GDM | Perry plos genetics 2012 |
| rs12970134 | MC4R | intergenic | 18 | 18q21.32 | A | G | 0.27 | T2D / BMI / waist circumference / insulin resistance | Chambers natgen 2008; Morris, naturegenetics 2012 |
| rs10401969 | SUGP1 | intron | 19 | 19p13.3 | C | T | 0.08 | T2D | Morris, naturegenetics 2012 |
| rs10423928 | GIPR | intron | 19 | 19q13.32 | A | T | 0.17 | 2hr glucose / T2D | Saxena et al. Nat Genet 2010 |
| rs8108269 | GIPR | intergenic | 19 | 19q13.32 | G | T | 0.31 | T2D | Morris, naturegenetics 2012 |
| rs6017317 | FITM2-R3HDML-HNF4A | intergenic | 20 | 20q13.12 | G | T | 0.18 (0.54) | Asian T2D | Cho natgen 2012 |
| rs5945326* | DUSP9 | intergenic | X | Xq28 | A | G | 0.79 | T2D / GDM | Voight et al DIAGRAM2 2010 |
| rs11605924* | CRY2 | intron | 11 | 11p11.2 | A | C | 1.04 | T2D | Dupuis et al Nat Genet 2010 |
| rs9939609 | FTO | intron | 16 | 16q12.2 | A | T | 1.20 | T2D, obesity | Frayling et al Nat Genet 2007 |
| rs17133918 | GRB10 | intron | 7 | 7p12.1 | C | T | | T2D | Prokopenko plos genetics 2013 |
| rs933360 | GRB10 | intron | 7 | 7p12.1 | A | G | | T2D | Prokopenko plos genetics 2013 |
| rs6943153 | GRB10 | intron | 7 | 7p12.1 | C | T | 0.0154 (beta) | fasting glucose /fasting insulin | Prokopenko plos genetics 2013 |
| rs7178572* | HMG20A | Intergenic | 15 | 7p12.1 | G | A | 1.09 | T2D / GDM | Perry plos genetics 2012; Kooner natgen 2012 |

**P4 Supplementary table 3. Association of T2D and GDM risk loci previously reported in the Indian population based studies with GDM risk in Indian and Sweden pregnant women. CHR = chromosome, BP = base pair coordinates, A1 = effect allele, n = study population size, OR = odds ratio (CI = 95% confidence intervals), P = two-tailed p-value for single test.**

| | | | | INDIA | | | SWEDEN | | |
|---|---|---|---|---|---|---|---|---|---|
| **CHR** | **SNP** | **BP** | **A1** | **n** | **OR (CI)** | **P** | **n** | **OR (CI)** | **P** |
| 7 | rs1799999 | 113878379 | A | 3664 | 0.77 (0.59 – 1.01) | 0.061 | 465 | 0.83 (0.48 – 1.43) | 0.50 |
| 20 | rs4812829 | 44360627 | A | 3576 | 0.85 (0.63 – 1.15) | 0.30 | 0 | NA | NA |
| 11 | rs689 | 2160994 | A | 3676 | 1.09 (0.78 – 0.57) | 0.60 | 489 | 1.101 (0.80 – 1.51) | 0.55 |
| 15 | rs7178572 | 77454848 | T | 3346 | 0.75 (0.57 – 0.98) | **0.03** | 476 | 0.8253 (0.59 – 1.15) | 0.25 |
| 13 | rs9552911 | 23290518 | A | 3665 | 0.85 (0.54 – 1.32) | 0.47 | 486 | 1.237 (0.11 – 13.76) | 0.86 |
| 2 | rs998451 | 134671718 | A | 3656 | 0.77 (0.52 – 1.13) | 0.18 | 482 | 1.068 (0.80 – 1.42) | 0.65 |

**P4 Supplementary table 4. Association of previously reported GDM risk loci discovered in the European population based studies with GDM risk in Indian and Sweden pregnant women. CHR = chromosome, BP = base pair coordinates, A1 = effect allele, n = study population size, OR = odds ratio, P = two-tailed p-value for single test.**

| | | | | INDIA | | | SWEDEN | | |
|---|---|---|---|---|---|---|---|---|---|
| CHR | SNP | BP | A1 | n | OR (CI) | P | n | OR (CI) | P |
| 4 | rs10010131 | 6291188 | A | 3617 | 0.81 (0.60 - 1.08) | 0.15 | 444 | 1.19 (0.88 - 1.63) | 0.25 |
| 9 | rs10811661 | 22134095 | C | 3666 | 1.01 (0.69 - 1.47) | 0.96 | 428 | 0.76 (0.47 - 1.22) | 0.25 |
| 10 | rs1111875 | 92703125 | G | 3675 | 1.02 (0.79 - 1.32) | 0.86 | 443 | 0.71 (0.52 - 0.97) | **0.031** |
| 3 | rs11708067 | 123346931 | G | 3648 | 1.29 (0.97 - 1.71) | 0.084 | 466 | 0.69 (0.48 -1.00) | 0.054 |
| 8 | rs13266634 | 117172544 | T | 3671 | 0.97 (0.72 - 1.31) | 0.84 | 458 | 0.88 (0.64 - 1.20) | 0.42 |
| 3 | rs1801282 | 12351626 | G | 3436 | 0.94 (0.63 - 1.40) | 0.76 | 421 | 1.32 (0.86 - 2.05) | 0.21 |
| 9 | rs2796441 | 81694033 | T | 3677 | 1.02 (0.79 - 1.32) | 0.88 | 457 | 1.00 (0.75 -1.34) | 0.98 |
| 3 | rs4402960 | 185793899 | T | 3535 | 0.89 (0.69 - 1.15) | 0.36 | 352 | 1.06 (0.73 - 1.53) | 0.77 |
| 11 | rs5219 | 17388025 | T | 3382 | 1.05 (0.81 - 1.36) | 0.73 | 264 | 1.09 (0.70 -1.67) | 0.71 |
| 2 | rs560887 | 168906638 | A | 3678 | 1.07 (0.74 - 1.56) | 0.71 | 383 | 0.80 (0.55 - 1.18) | 0.26 |
| 6 | rs7754840 | 20661019 | C | 3502 | 1.19 (0.90 - 1.57) | 0.22 | 426 | 0.97 (0.71 - 1.32) | 0.83 |
| 6 | rs7756992 | 20679478 | G | 3469 | 1.16 (0.88 - 1.54) | 0.29 | 425 | 0.96 (0.70 -1.32) | 0.79 |
| 10 | rs7903146 | 112998590 | T | 3330 | 1.29 (0.98 - 1.72) | 0.072 | 373 | 1.20 (0.84 - 1.70) | 0.31 |
| 16 | rs9939609 | 53786615 | A | 2962 | 0.79 (0.57 - 1.10) | 0.16 | 0 | NA | NA |

**P4 Supplementary table 5. Association of previously reported T2D risk loci discovered in the European population based studies with GDM risk in Indian and Sweden pregnant women. CHR = chromosome, BP = base pair coordinates, A1 = effect allele, n = study population size, OR = odds ratio, P = two-tailed p-value for single test.**

| | | | INDIA | | | SWEDEN | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CHR | SNP | A1 | n | OR | P | n | OR | P | GENE / nearest Gene | location | Chr | locus | RA | OA |
| 1 | rs2296172 | G | 3618 | 0.89 (0.58 - 1.37) | 0.61 | 385 | 0.98 (0.67-1.45) | 0.94 | MACF1 | coding - missense | 1 | 1p34.3 | G | A |
| 1 | rs340874 | A | 3490 | 1.13 (0.87 - 1.47) | 0.35 | 427 | 0.92 (0.68-1.24) | 0.58 | PROX1 | intergenic | 1 | 1q41 | C | T |
| 2 | rs13389219 | T | 3605 | 0.79 (0.59 - 1.08) | 0.14 | 475 | 1.13 (0.85-1.51) | 0.4 | GRB14 | intergenic | 2 | 2q24.3 | C | T |
| 2 | rs243088 | T | 3497 | 1.29 (0.99 - 1.68) | 0.06 | 425 | 1.13 (0.83-1.55) | 0.41 | BCL11A | intergenic | 2 | 2p16.1 | T | A |
| 2 | rs2943641 | T | 3429 | 1.06 (0.78 - 1.43) | 0.7 | 424 | 0.89 (0.66-1.21) | 0.45 | IRS1 | intergenic | 2 | 2q36.3 | C | T |
| 2 | rs4675095 | T | 3594 | 0.77 (0.51 - 1.17) | 0.22 | 460 | 1.39 (0.74-2.61) | 0.29 | IRS1 | intron | 2 | 2q36.3 | A | T |
| 2 | rs7578326 | G | 3390 | 1.06 (0.78 - 1.43) | 0.72 | 492 | 1.018 (0.76-1.35) | 0.9 | KIAA1486/IRS1 | intergenic | 2 | 2q36.3 | A | G |
| 2 | rs7578597 | C | 3490 | 1.34 (0.95 - 1.89) | 0.09 | 423 | 1.041 (0.58-1.86) | 0.89 | THADA | coding - missense | 2 | 2p21 | T | C |
| 2 | rs7593730 | T | 3673 | 0.87 (0.63 - 1.21) | **0.4** | 457 | 0.97 (0.68-1.37) | 0.86 | RBMS1/ITGB6 | intronic | 2 | 9q24.2 | T | C |
| 2 | rs7607980 | C | 3657 | 1.08 (0.72 - 1.62) | 0.69 | 453 | 0.93 (0.59-1.47) | 0.77 | COBL1 | coding - missense | 2 | 2q24.3 | C | T |
| 3 | rs11920090 | A | 3395 | 0.74 (0.50 - 1.01) | 0.13 | 491 | 1.08 (0.70-1.65) | 0.74 | SLC2A2 | intron | 3 | 3q26.2 | T | A |
| 3 | rs4607103 | C | 3659 | 1.23 (0.95 - 1.59) | 0.11 | 430 | 1.1 (0.77-1.57) | 0.6 | ADAMTS9-AS2 | intron | 3 | 3p14.1 | C | T |
| 3 | rs831571 | T | 3505 | 0.93 (0.67 - 1.28) | 0.64 | 425 | 0.94 (0.63-1.41) | 0.79 | PSMD6 | intergenic | 3 | 3p14.1 | C | T |
| 4 | rs6815464 | G | 3503 | 0.98 (0.68 - 1.41) | 0.91 | 426 | 0.52 (0.15-1.82) | 0.3 | MAEA | intron | 4 | 4p16.3 | C | G |
| 5 | rs4457053 | G | 3370 | 1.11 (0.82 - 1.52) | 0.49 | 488 | 1.16 (0.85-1.59) | 0.32 | ZBED3 | intron of ZBED3-AS1 | 5 | 5q13.3 | G | A |
| 5 | rs459193 | T | 3655 | 0.88 (0.67 - 1.15) | 0.33 | 469 | 1.33 (0.94-1.88) | 0.09 | ANKRD55 | intergenic | 5 | 5q11.2 | G | A |
| 6 | rs9470794 | C | 3397 | 0.77 (0.50 - 1.19) | 0.23 | 491 | 1.03 (0.61-1.75) | 0.89 | ZFAND3 | intron | 6 | 6p21.2 | C | T |
| 7 | rs17133918 | T | 3681 | 0.99 (0.75 - 1.32) | 0.96 | 459 | 0.91 (0.67-1.22) | 0.51 | GRB10 | intron | 7 | 7p12.1 | C | T |
| 7 | rs17168486 | T | 3632 | 0.84 (0.63 - 1.11) | 0.21 | 436 | 1.32 (0.90-1.92) | 0.15 | DGKB | intergenic | 7 | 7p21.2 | T | C |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | rs2191349 | G | 3675 | 0.89 (0.68 - 1.16) | 0.37 | 454 | 1.22 (0.91-1.64) | 0.18 | DGKB/TMEM195 | intergenic | 7 | 7p21.2 | T | G |
| 7 | rs4607517 | A | 3671 | 1.09 (0.76 - 1.59) | 0.62 | 456 | 1.13 (0.78-1.61) | 0.52 | GCK | intergenic | 7 | 7p13 | A | G |
| 7 | rs6467136 | A | 3375 | 0.79 (0.61 - 1.03) | 0.08 | 382 | 1.11 (0.82-1.50) | 0.47 | GCC1-PAX4 | intergenic | 7 | 7q32.1 | G | A |
| 7 | rs6943153 | T | 3391 | 0.78 (0.58 - 1.04) | 0.08 | 492 | 1.03 (0.75-1.40) | 0.85 | GRB10 | intron | 7 | 7p12.1 | C | T |
| 7 | rs864745 | G | 3651 | 0.99 (0.74 - 1.31) | 0.91 | 451 | 0.93 (0.68-1.26) | 0.65 | JAZF1 | intron | 7 | 7p15.1 | T | C |
| 7 | rs933360 | G | 3674 | 0.89 (0.68 - 1.17) | 0.41 | 0 | NA (NA-NA) | NA | GRB10 | intron | 7 | 7p12.1 | A | G |
| 8 | rs516946 | A | 3687 | 0.88 (0.63 - 1.23) | 0.45 | 457 | 1.16 (0.83-1.63) | 0.37 | ANK1 | intron | 8 | 8p11.21 | C | T |
| 8 | rs896854 | A | 3674 | 0.82 (0.63 - 1.07) | 0.14 | 481 | 0.97 (0.72-1.30) | 0.83 | TP53INP1 | intron | 8 | 8q22.1 | T | C |
| 9 | rs13292136 | T | 3490 | 1.16 (0.82 - 1.63) | 0.4 | 427 | 0.78 (0.47-1.32) | 0.35 | TLE4 (CHCHD9) | intergenic | 9 | 9q21.31 | C | T |
| 9 | rs7034200 | C | 3642 | 1.035 (0.79 - 1.34) | 0.79 | 449 | 1.17 (0.86-1.58) | 0.3 | GLIS3 | intron | 9 | 9q24.2 | A | C |
| 10 | rs10885122 | T | 3465 | 0.95 (0.68 - 1.32) | 0.76 | 424 | 0.96 (0.61-1.51) | 0.85 | ADRA2A | intergenic | 10 | 10q25.2 | G | T |
| 10 | rs12571751 | G | 3390 | 1.24 (0.95 - 1.61) | 0.11 | 492 | 1.39 (1.05-1.83) | **0.021** | ZMIZ1 | intron | 10 | 10q22.3 | A | G |
| 10 | rs553668 | 0 | 0 | NA (NA - NA) | NA | 474 | 1.03 (0.67-1.57) | 0.9 | ADRA2A | UTR-3 | 10 | 10q25.2 | A | G |
| 11 | rs10830963 | G | 3495 | 0.94 (0.72 - 1.2) | 0.65 | 425 | 1.03 (0.75-1.413) | 0.85 | MTNR1B | intron | 11 | 11q14.3 | G | C |
| 11 | rs11605924 | A | 3679 | 0.67 (0.52 - 0.87) | **0.0026** | 484 | 1.44 (1.08-1.91) | **0.0129** | CRY2 | intron | 11 | 11p11.2 | A | C |
| 11 | rs1552224 | G | 3679 | 0.94 (0.67 - 1.34) | 0.73 | 385 | 1.14 (0.76-1.70) | 0.52 | CENTD2 | intergenic | 11 | 11q13.4 | A | C |
| 11 | rs163184 | T | 3491 | 1.22 (0.94 - 1.60) | 0.13 | 0 | NA (NA-NA) | NA | KCNQ1 | intron | 11 | 11p15.4 | G | T |
| 11 | rs174550 | C | 3676 | 1.02 (0.73 - 1.43) | 0.91 | 379 | 0.96 (0.67-1.37) | 0.83 | FADS1 | intron | 11 | 11q12.2 | T | C |
| 11 | rs2237895 | C | 3463 | 0.81 (0.62 - 1.06) | 0.13 | 410 | 1.43 (1.06-1.94) | **0.0204** | KCNQ1 | intron | 11 | 11p15.4 | C | T |
| 11 | rs7944584 | T | 3343 | 0.93 (0.66 - 1.32) | 0.69 | 413 | 0.82 (0.57-1.17) | 0.26 | MADD | intron | 11 | 11p11.2 | A | T |
| 12 | rs10842994 | T | 3675 | 1.06 (0.73 - 1.52) | 0.77 | 481 | 0.79 (0.53-1.16) | 0.22 | KLHDC5 | intergenic | 12 | 12p11.22 | C | T |
| 12 | rs11063069 | G | 3454 | 0.89 (0.61 - 1.30) | 0.55 | 418 | 1.11 (0.76-1.60) | 0.59 | CCND2 | intergenic | 12 | 12p13.32 | G | A |
| 12 | rs1153188 | A | 3680 | 0.87 (0.61 - 1.23) | 0.42 | 385 | 1.08 (0.74-1.58) | 0.67 | DCD | intergenic | 12 | 12q13.2 | A | T |
| 12 | rs1531343 | C | 3683 | 0.87 (0.62 - 1.23) | 0.42 | 457 | 1.61 (0.96-2.68) | 0.069 | HMGA2 | intron of pseudogene | 12 | 12q14.3 | C | G |
| 12 | rs35767 | T | 3678 | 0.96 (0.70 - 1.31) | 0.79 | 384 | 1.16 (0.76-1.76) | 0.47 | IGF1 | nearGene-5 | 12 | 12q23.2 | G | A |
| 12 | rs7957197 | A | 3689 | 1.18 (0.72 - 1.91) | 0.5 | 448 | 0.75 (0.51-1.11) | 0.15 | OASL/TCF1/HNF1A | intron of OASL | 12 | 12q24.31 | T | A |
| 12 | rs7961581 | C | 3486 | 0.85 (0.64 - 1.13) | 0.27 | 421 | 0.95 (0.67-1.35) | 0.79 | TSPAN8,LGR5 | intergenic | 12 | 12q21.1 | C | T |
| 15 | rs11071657 | G | 3669 | 0.91 (0.67 - 1.21) | 0.51 | 456 | 0.88 (0.65-1.18) | 0.38 | FAM148B | intergenic | 15 | 15q22.2 | A | G |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | rs11634397 | A | 3678 | 1.01 (0.78 - 1.31) | 0.92 | 457 | 1.23 (0.91-1.65) | 0.17 | ZFAND6 | intergenic | 15 | 15q25.1 | G | A |
| 15 | rs17271305 | G | 3597 | 0.98 (0.74 - 1.30) | 0.9 | 478 | 0.90 (0.68-1.19) | 0.47 | VPS13C | intron | 15 | 15q22.2 | G | A |
| 15 | rs7177055 | G | 3680 | 0.74 (0.57 - 0.96) | **0.024** | 457 | 0.91 (0.65-1.27) | 0.58 | HMG20A | intergenic | 15 | 15q24.3 | A | G |
| 15 | rs8042680 | C | 3662 | 1.08 (0.83 - 1.40) | 0.57 | 456 | 0.89 (0.65-1.22) | 0.48 | PRC1 | intron | 15 | 15q26.1 | A | C |
| 16 | rs7202877 | G | 3684 | 1.06 (0.66 - 1.68) | 0.81 | 0 | NA (NA-NA) | NA | BCAR1 | intergenic | 16 | 16q23.1 | T | G |
| 18 | rs8090011 | G | 3683 | 1.02 (0.79 - 1.32) | 0.89 | 457 | 1.49 (1.11-2.01) | **0.009** | LAMA1 | intron | 18 | 18p11.31 | G | C |
| 19 | rs10401969 | C | 3393 | 1.05 (0.68 - 1.6) | 0.83 | 491 | 1.06 (0.67-1.70) | 0.79 | SUGP1 | intron | 19 | 19p13.3 | C | T |
| 19 | rs10423928 | A | 3681 | 0.90 (0.62 - 1.31) | 0.58 | 480 | 1.06 (0.76-1.47) | 0.72 | GIPR | intron | 19 | 19q13.32 | A | T |
| 19 | rs8108269 | G | 3293 | 1.08 (0.82 - 1.43) | 0.58 | 429 | 0.78 (0.57-1.08) | 0.13 | GIPR | intergenic | 19 | 19q13.32 | G | T |
| 20 | rs6017317 | G | 3530 | 0.96 (0.72 - 1.26) | 0.74 | 451 | 1.05 (0.73-1.52) | 0.78 | FITM2-R3HDML-HNF4A | intergenic | 20 | 20q13.12 | G | T |
| 23 | rs5945326 | G | 3377 | 1.15 (0.88 - 1.50) | 0.29 | 495 | 0.69 (0.49-0.98) | **0.035** | DUSP9 | intergenic | X | Xq28 | A | G |

**P4 Supplementary table 6. Association of Indian / Swedish GDM loci (from the present study) with glycemic traits. Chr = chromosome, EA = effect allele, B = beta / effect size, SE = standard error, p = p-values.**

| | | | | | Fasting Glucose | | 2 hour glucose | | Fasting insulin | | 2 hour insulin | | HOMA2-B | | HOMA2-IR | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNP | locus | location | Chr | EA | B (SE) | p | B (SE) | p | B (SE) | p | B (SE) | p | B (SE) | p | B | p |
| RS7178572 | HMG20A | intergenic | 15 | T | 0.026 (0.14) | 0.85 | -0.07 (0.10) | 0.49 | 0.09 (0.11) | 0.41 | -0.13 (0.12) | 0.27 | -0.29 (0.10) | 0.053 | -0.03 (0.18) | 0.87 |
| RS1799999 | PP1G.G | coding | 7 | C | 0.36 (0.28) | 0.22 | 0.26 (0.17) | 0.13 | -0.19 (0.24) | 0.43 | -0.57 (0.22) | 0.02 | 0.09 (0.21) | 0.67 | 0.12 (0.24) | 0.62 |
| rs1111875 | HHEX/IDE | intergenic | 10 | G | -0.05 (0.14) | 0.73 | -0.11 (0.10) | 0.30 | 0.01 (0.11) | 0.97 | -.05 (0.12) | 0.67 | -0.04 (0.11) | 0.71 | 0.13 (0.16) | 0.45 |
| rs11708067 | ADCY5 | intron | 3 | G | 0.18 (0.16) | 0.30 | 0.31 (0.14) | 0.037 | 0.33 (0.16) | 0.057 | 0.184 (0.17) | 0.29 | -0.40 (0.14) | 0.010 | 0.18 (0.19) | 0.35 |
| rs11605924 | CRY2 | intron | 11 | A | 0.13 (0.19) | 0.49 | -0.06 (0.13) | 0.64 | 0.19 (0.15) | 0.202 | 0.09 (0.14) | 0.53 | -0.24 (0.14) | 0.096 | -0.26 (0.19) | 0.20 |
| rs12571751 | ZMIZ1 | intron | 10 | G | -0.12 (0.17) | 0.51 | 0.022 (0.12) | 0.86 | -0.19 (0.13) | 0.18 | -0.11 (0.14) | 0.43 | 0.09 (0.13) | 0.47 | -0.15 (0.19) | 0.45 |
| rs2237895 | KCNQ1 | intron | 11 | C | -0.12 (0.15) | 0.45 | -0.185 (0.11) | 0.11 | 0.17 (0.12) | 0.17 | 0.09 (0.13) | 0.49 | -0.04 (0.11) | 0.70 | -0.12 (0.18) | 0.51 |
| rs8090011 | LAMA1 | intron | 18 | G | -0.19 (0.15) | 0.23 | -0.215 (0.12) | 0.08 | -0.10 (0.12) | 0.42 | -0.28 (0.13) | 0.044 | 0.19 (0.11) | 0.11 | -0.15 (0.18) | 0.41 |
| rs5945326 | DUSP9 | intergenic | X | G | -0.11 (0.16) | 0.51 | 0.04 (0.12) | 0.78 | -0.12 (0.14) | 0.37 | -0.15 (0.13) | 0.28 | 0.24 (0.12) | 0.059 | 0.06 (0.20) | 0.77 |
| rs7593730 | RBMS1/ITGB6 | intronic | 2 | T | -0.14 (0.18) | 0.43 | -0.078 (0.13) | 0.54 | -.14 (0.13) | 0.30 | -0.25 (0.15) | 0.19 | 0.18 (0.13) | 0.19 | -0.25 (0.22) | 0.27 |
| rs243088 | BCL11A | intergenic | 2 | T | -0.24 (0.11) | 0.03 | 0.003 (0.04) | 0.93 | -0.11 (0.11) | 0.30 | 0.016 (0.12) | 0.90 | 0.09 (0.11) | 0.42 | 0.09 (0.12) | 0.44 |
| rs7177055 | HMG20A | intergenic | 15 | G | .026 (0.09) | 0.78 | -0.01 (0.01) | 0.57 | 0.08 (0.09) | 0.39 | 0.037 (0.10) | 0.72 | -0.13 (0.09) | 0.68 | 0.13 (0.11) | 0.26 |

**P4 Supplementary table 7: eQTL expression in human pancreatic islets**

| SNP | gene | beta | t-stat | p-value | FDR |
|---|---|---|---|---|---|
| rs7178572 | *PSTPIP1* | 0.395195763 | 3.858312945 | 0.000157308 | **0.003775392** |
| rs7178572 | *HMG20A* | 0.365641775 | 3.482768383 | 0.000618591 | **0.007423092** |
| rs7178572 | *ENSG00000260787* | 0.307698831 | 2.873430187 | 0.004532857 | **0.03626286** |
| rs1111875 | *NHP2P1* | 0.329797925 | 3.133224821 | 0.00200908 | **0.02109534** |
| rs1111875 | *BTAF1* | 0.281148227 | 2.620336099 | 0.009510171 | **0.02109534** |
| rs1111875 | *MARK2P9* | -0.26192091 | 2.456599276 | 0.014943273 | 0.0665712 |
| rs1111875 | *FGFBP3* | 0.246821227 | -2.26902637 | 0.024414953 | 0.07845218 |
| rs11605924 | *AC044839.2* | 0.263122055 | 2.519988934 | 0.012577208 | 0.3441981 |
| rs11605924 | *CHRM4* | 0.230781992 | 2.150044451 | 0.03284293 | 0.3441981 |
| rs11605924 | *CRY2* | 0.216356367 | 2.028259999 | 0.043959902 | 0.3441981 |
| rs11605924 | *PEX16* | 0.211971204 | 1.980062519 | 0.049171156 | 0.3441981 |
| rs8090011 | *LOC101927188* | 0.22180716 | 2.12837551 | 0.034622273 | 0.2077336 |
| rs8090011 | *LAMA1* | 0.170865025 | 1.617093531 | 0.107552781 | 0.3226583 |
| rs2237895 | *SLC22A18AS* | 0.201179621 | 1.983395139 | 0.048794719 | 0.7267382 |
| rs2237895 | *KCNQ1OT1* | 0.207588021 | 1.981981383 | 0.048954112 | 0.7267382 |

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*"Coming together is a beginning, keeping together is progress; working together is success."*
**Henry Ford**

**Dr. Geeti Puri Arora M.D**
Consultant Physician and Diabetologist

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