Paleolithic Diet, Abdominal Adiposity, and Systemic Low-grade Chronic Inflammation. Associations in Observational Studies and a Randomized Controlled Trial

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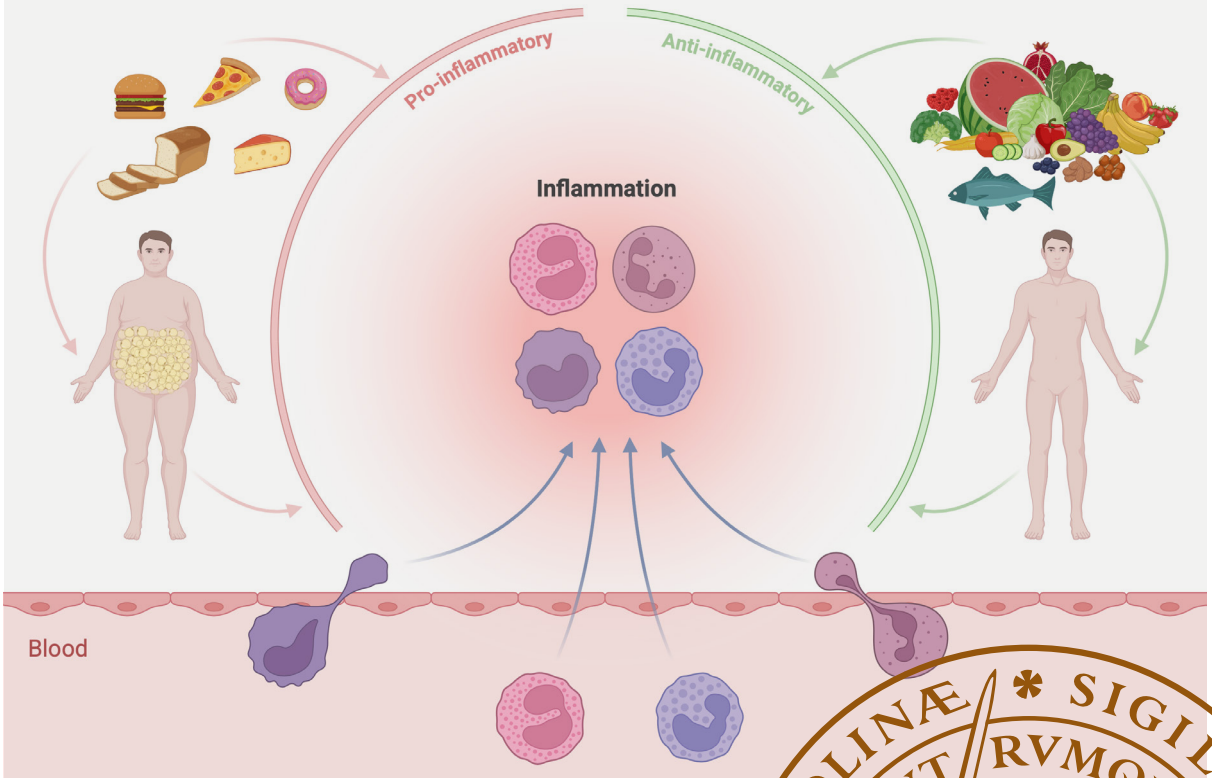

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Pedro Carrera Bastos

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Paleolithic Diet, Abdominal Adiposity, and Systemic Low-grade Chronic Inflammation. Associations in Observational Studies and a Randomized Controlled Trial

Abstract:

Background: Systemic low-grade chronic inflammation (SLGCI), commonly assessed by biomarkers such as total leukocyte count, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP), is associated with cardiometabolic disease, and both are associated with diet and abdominal adiposity. The Paleolithic diet may reduce SLGCI by reducing abdominal adiposity and through direct effects on the immune system.
Aims: This thesis explores the relationship between SLGCI, abdominal adiposity, and the Paleolithic diet using both observational and interventional designs.
Methods: Papers I and II compared CRP and total adiponectin (an adipokine often inversely associated with SLGCI, abdominal adiposity, and cardiometabolic disease) between Kitavans, a lean Melanesian population with a Paleolithic-type diet and an apparent absence of cardiometabolic disease, and Swedish controls. Paper III was a 2-year RCT comparing a healthy diet without cereal grains, a main characteristic of the Paleolithic diet, versus one emphasizing whole grains, each with and without long-term exercise, on waist circumference, a proxy for abdominal adiposity. Paper IV analyzed associations between the Paleolithic Diet Fraction (PDF), a dietary pattern measure defined as the proportion of food intake consistent with a Paleolithic diet, and inflammatory biomarkers (total leukocyte count, NLR, and CRP) in 23,250 participants from the Malmö Diet and Cancer Study.
Results: In Papers I and II, Kitavans had lower CRP and lower total adiponectin than Swedish controls. In Paper III, the no-grain group without exercise showed the largest, albeit non-significant, reduction in waist circumference. In Paper IV, PDF was inversely associated with all inflammatory biomarkers, independent of adiposity and lifestyle factors.
Conclusion: A relatively higher intake of Paleolithic foods is associated with lower levels of SLGCI, potentially through both reduced abdominal adiposity and direct effects on the immune system. The low adiponectin levels among Kitavans raise questions about its presumed inverse association with SLGCI, abdominal adiposity, and cardiometabolic disease.
Key words: Systemic Low-Grade Chronic Inflammation, Paleolithic Diet, C-Reactive Protein, Adiponectin, Waist Circumference.

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MADE IN SWEDEN

To the memory of

***Staffan Lindeberg**, dear friend, mentor, and the one who showed me what science can be: honest, humble, and fueled by wonder. Your influence shaped every step of this journey.*

***Fernando Carrera** ("Tio Fernando"), brilliant physician, passionate and wide-ranging thinker, and beloved uncle, who taught me that discipline, ethics, and an enduring curiosity can shape not just a career, but a life.*

Table of Contents

Abstract

Background:

Systemic low-grade chronic inflammation (SLGCI), commonly assessed by biomarkers such as total leukocyte count, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP), is associated with cardiometabolic disease, and both are associated with diet and abdominal adiposity. The Paleolithic diet may reduce SLGCI by reducing abdominal adiposity and through direct effects on the immune system.

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Populärvetenskaplig sammanfattning

Låggradig kronisk inflammation är en mild ihållande aktivering av immunsystemet som är kopplad till kardiometabol sjukdom såsom typ 2-diabetes och hjärt-kärlsjukdom. Kost och bukfetma är också kopplat till låggradig kronisk inflammation och kardiometabol sjukdom. Paleolitisk kost tros kunna minska låggradig kronisk inflammation både genom att reducera bukfetma och genom direkta effekter på immunsystemet. Paleolitisk kost liknar den kost våra paleolitiska förfäder åt och betonar naturliga, obearbetade livsmedel såsom frukt, grönsaker, rotfrukter, nötter, ägg, kött och fisk, samtidigt som moderna inslag såsom spannmål, mejeriprodukter, tillsatt socker och ultraprocessade livsmedel utesluts. Denna avhandling undersöker sambanden mellan låggradig kronisk inflammation, bukfetma, och paleolitisk kost med hjälp av både observations- och interventionsstudier (Studie I–IV):

- Studierna I och II jämförde blodmarkörer mellan personer som lever på ön Kitava i Papua Nya Guinea—en slank befolkning utan kardiometabol sjukdom som äter en kost som liknar paleolitisk kost—och svenska personer som matchats med Kitavanerna avseende ålder och kön. Kitavanerna hade lägre nivåer av C-reaktivt protein (CRP), en biomarkör för låggradig kronisk inflammation, samt lägre nivåer av adiponektin, ett hormon som utsöndras av fettväv och som är omvänt kopplat till låggradig kronisk inflammation, bukfetma, och kardiometabol sjukdom.
- Studie III var en tvåårig randomiserad kontrollerad studie inom svensk primärvård. Studien jämförde effekt på midjemåttet av två hälsosamma koster, en utan spannmål och en som betonade fullkorn, i kombination med eller utan långsiktig fysisk träning. Den största minskningen av midjemåttet sågs i gruppen som uteslöt spannmål ur kosten och inte tränade. Skillnaden var dock inte statistiskt säkerställd, vilket troligen berodde på ett otillräckligt antal deltagare i studien.
- Studie IV analyserade data från 23 250 vuxna i Malmö Kost Cancer-studien. Resultaten visade att personer med högre Paleolithic Diet Fraction (PDF), ett mått på hur stor del av matintaget som består av paleolitisk kost, hade lägre nivåer av låggradig kronisk inflammation, mätt som totalt antal vita blodkroppar, kvoten mellan neutrofila och lymfocytära vita blodkroppar, samt CRP, oberoende av kroppsfett och livsstilsfaktorer.

Sammantaget tyder resultaten på att relativt sett högre intag av paleolitisk kost är kopplat till lägre nivåer av låggradig kronisk inflammation, och att sambandet kan förklaras både av minskad bukfetma och av direkta effekter av kosten på immunsystemet. Kitavanernas låga nivåer av adiponektin ifrågasätter dess förmodade omvända koppling till låggradig kronisk inflammation, bukfetma, och kardiometabol sjukdom.

Lay summary

Systemic low-grade chronic inflammation (SLGCI) is a mild, persistent activation of the immune system linked to cardiometabolic disease such as type 2 diabetes and cardiovascular disease. Diet and abdominal adiposity are also associated with SLGCI and cardiometabolic disease. The Paleolithic diet is believed to reduce SLGCI both by reducing abdominal adiposity and by direct effects on the immune system. The Paleolithic diet resembles the diet of our Paleolithic ancestors and emphasizes natural, unprocessed foods such as fruits, vegetables, tubers, nuts, eggs, meat, and fish, while excluding modern elements such as grains, dairy products, added sugar, and ultra-processed foods. This thesis investigates the associations between SLGCI, abdominal adiposity, and the Paleolithic diet using both observational and interventional studies (Studies I–IV):

- Studies I and II compared blood biomarkers between individuals living on the island of Kitava in Papua New Guinea—a lean population without cardiometabolic disease and with a Paleolithic-type diet—and Swedish individuals matched to the Kitavans by age and sex. The Kitavans had lower levels of C-reactive protein (CRP), a biomarker of SLGCI, as well as lower levels of adiponectin, a hormone secreted by fat tissue that is inversely associated with SLGCI, abdominal adiposity, and cardiometabolic disease.
- Study III was a 2-year randomized controlled trial carried out in Swedish primary care. The study compared the effects on waist circumference of two healthy diets, one that excluded cereal grains and one that emphasized whole grains, in combination with or without long-term physical exercise. The greatest reduction in waist circumference was observed in the group that excluded cereal grains and did not exercise. However, the difference was not statistically significant, likely due to an insufficient number of study participants.
- Study IV analyzed data from 23,250 adults in the Malmö Diet and Cancer Study. The results showed that individuals with a higher Paleolithic Diet Fraction (PDF), a measure of the proportion of the food intake made up of the Paleolithic diet, had lower levels of SLGCI, measured by total white blood cell count, the neutrophil-to-lymphocyte ratio, and CRP, independent of body fat and lifestyle factors.

In summary, the results suggest that a relatively higher intake of a Paleolithic diet is associated with lower levels of SLGCI, and that this association may be explained both by reduced abdominal adiposity and by direct effects of the diet on the immune system. The low adiponectin levels among Kitavans question its supposed inverse association with SLGCI, abdominal adiposity, and cardiometabolic disease.

List of papers

Paper I

Carrera-Bastos, P., Fontes-Villalba, M., Gurven, M., Muskiet, F. A. J., Åkerfeldt, T., Lindblad, U., Råstam, L., Frostegård, J., Shapira, Y., Shoenfeld, Y., Granfeldt, Y., Sundquist, K., & Jönsson, T. (2020). C-reactive protein in traditional melanesians on Kitava. BMC Cardiovascular Disorders, 20(1), 524. https://doi.org/10.1186/s12872-020-01812-7

Paper II

Carrera-Bastos, P., Fontes-Villalba, M., Ahrén, B., Lindblad, U., Råstam, L., Frostegård, J., Åkerfeldt, T., Granfeldt, Y., Sundquist, K., & Jönsson, T. (2024). Total adiponectin in indigenous Melanesians on Kitava. American Journal of Human Biology: The Official Journal of the Human Biology Council, 36(10), e24134. https://doi.org/10.1002/ajhb.24134

Paper III

Carrera-Bastos, P., Rydhög, B., Fontes-Villalba, M., Arvidsson, D., Granfeldt, Y., Sundquist, K., & Jönsson, T. (2024). Randomised controlled trial of lifestyle interventions for abdominal obesity in primary health care. Primary Health Care Research & Development, 25, e19. https://doi.org/10.1017/S1463423624000069

Paper IV

Carrera-Bastos, P., Rydhög, B., Granfeldt, Y., Sundquist, K., Sonestedt, E., Nilsson, P. M., & Jönsson, T. Association between Paleolithic Diet Fraction and Systemic Low-Grade Chronic Inflammation in the Malmö Diet and Cancer Study Cohort. Submitted. 2025.

Authors' contribution to the papers

Paper I

Pedro Carrera-Bastos and Tommy Jönsson conceived of and designed the study, analyzed and interpreted the data, and wrote the manuscript. Torbjörn Åkerfeldt, Ulf Lindblad, Lennart Råstam, Johan Frostegård, Yinon Shapira, and Yehuda Shoenfeld contributed to data acquisition, analysis, interpretation, and manuscript revision. Maelán Fontes-Villalba, Michael Gurven, Frits A. J. Muskiet, Yvonne Granfeldt, and Kristina Sundquist provided critical revisions of the manuscript. All authors read and approved the final version.

Paper II

Pedro Carrera-Bastos and Tommy Jönsson conceived of and designed the study, analyzed and interpreted the data, and wrote the manuscript. Bo Ahrén, Ulf Lindblad, Lennart Råstam, Johan Frostegård, and Torbjörn Åkerfeldt contributed to data acquisition, analysis, interpretation, and manuscript revision. Maelán Fontes-Villalba, Yvonne Granfeldt, and Kristina Sundquist provided critical revisions of the manuscript. All authors read and approved the final version.

Paper III

Pedro Carrera-Bastos and Tommy Jönsson conceived of and designed the study, analyzed and interpreted the data, and wrote the manuscript. Daniel Arvidsson and Yvonne Granfeldt contributed to study design, data acquisition, analysis, interpretation, and manuscript revision. Björn Rydhög, Maelán Fontes-Villalba, and Kristina Sundquist provided critical revisions of the manuscript. All authors read and approved the final version.

Paper IV

Pedro Carrera-Bastos and Tommy Jönsson conceived of and designed the study, analyzed and interpreted the data, and wrote the manuscript. Björn Rydhög, Yvonne Granfeldt, Kristina Sundquist, Emily Sonestedt, and Peter M. Nilsson provided critical revisions of the manuscript. All authors read and approved the final version.

Abbreviations

BMI	Body mass index
CRP	C-reactive protein
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostatic model assessment of insulin resistance
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-17	Interleukin-17
LDL	Low-density lipoprotein
lnCRP	Natural logarithm of CRP
LPS	Lipopolysaccharide
MDCS	Malmö Diet and Cancer Study
MVPA	Moderate-to-vigorous physical activity
NF-κB	Nuclear factor kappa B
NLR	Neutrophil-to-lymphocyte ratio
PDF	Paleolithic Diet Fraction
PC	Phosphorylcholine
RCT	Randomized controlled trial
SED	Sedentary time
SLGCI	Systemic low-grade chronic inflammation
TNF-α	Tumor necrosis factor alpha

Introduction

Inflammation

Overview

The term inflammation originates from the Latin *inflammare*, meaning to ignite or burn [1]. The metaphor of burning pain aligns with the classical cardinal signs of inflammation (redness, swelling, heat, and pain) first described over 2,000 years ago [2]. Despite this destructive connotation, inflammation is a phylogenetically conserved physiological process that has been maintained and refined through evolutionary pressures due to its survival advantage: it enables the host to eliminate microbial threats, neutralize harmful stimuli, and initiate tissue repair [3–6].

This complex response involves the coordinated activation of both immune and non-immune cells, including macrophages, mast cells, neutrophils, monocytes, dendritic cells, fibroblasts, and endothelial cells [3–8]. It also demands significant metabolic resources, as evidenced by alterations in glucose and lipid metabolism and the activation of hormonal axes [9,10]. While such adaptations are beneficial in the context of time-limited acute inflammation [3,9], they may become maladaptive when inflammation becomes chronic. Prolonged inflammation can ultimately compromise both survival and reproductive success in the host [9,10].

Chronic inflammation may present in various forms, including localized tissue inflammation, systemic high-grade inflammation (as observed in certain infectious and autoimmune diseases), or systemic low-grade chronic inflammation (SLGCI) [3,11].

Systemic low-grade chronic inflammation

SLGCI is characterized by persistent low-level activation of the immune system. Innate immune cells, including monocytes, macrophages, and neutrophils, chronically secrete bioactive molecules, notably pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumor necrosis factor-α (TNF-α) [3,11,12]. This chronic cytokine activity may interfere with insulin signaling, impair endothelial function, and promote hyperglycemia, dyslipidemia, atheromatous plaque expansion and rupture, and thrombosis [13–16]. These mechanisms help explain the associations

between SLGCI and cardiometabolic diseases such as type 2 diabetes [13] and cardiovascular disease [16], both of which rank among the leading causes of global morbidity and mortality [17,18].

SLGCI is quantified by measuring circulating biomarkers that reflect persistent immune activation, hereafter referred to as inflammatory biomarkers [3,11,19,20]. In the context of SLGCI, these biomarkers are typically moderately elevated, that is, higher than physiological baseline levels but below the pronounced increases observed in acute inflammation [11,19,20]. Among these inflammatory biomarkers, C-reactive protein (CRP), total leukocyte count, and the neutrophil-to-lymphocyte ratio (NLR) have been extensively used in both clinical and epidemiological studies [21–41].

CRP is an acute-phase reactant synthesized by hepatocytes in response to cytokine stimulation, particularly IL-6 [42]. Functionally, CRP contributes to innate immunity by binding to phosphocholine residues on microbial surfaces and apoptotic cells, facilitating their clearance through opsonization and complement activation [43,44]. In SLGCI, CRP levels typically remain below 10 mg/L [20], whereas in acute inflammatory states, such as infections, they often exceed this threshold and can rise above 100 mg/L in severe cases [45]. Elevated CRP concentrations have been associated with increased risk of cardiovascular disease [20,29], type 2 diabetes [23,29], and both cardiovascular and all-cause mortality [21,22].

Total leukocyte count is another marker of systemic inflammation [28]. Leukocytes, or white blood cells, include multiple immune cell types, such as neutrophils, lymphocytes, and monocytes, each contributing to immune surveillance, pathogen defense, and inflammatory responses [46]. Elevated total leukocyte counts, even within the upper end of the normal range but below the threshold for leukocytosis (i.e., $< 11 \times 10^9$/L) [47], have been associated with higher risk of cardiometabolic diseases [29–35].

NLR, which reflects the balance between innate and adaptive immune responses, is also a widely used biomarker of systemic inflammation [39,48]. Neutrophils, a key component of the innate immune system, play a central role in first-line defense against infections and tissue damage [46]. Upon activation, neutrophils rapidly migrate to affected sites, where they participate in pathogen clearance and tissue remodeling through phagocytosis, degranulation, and the release of reactive oxygen species, proteolytic enzymes, and pro-inflammatory cytokines [46]. While these functions are essential for host defense, excessive or prolonged neutrophil activity, as observed in chronic inflammation, can exacerbate oxidative stress and cause collateral tissue injury [46,48]. Lymphocytes, in contrast, are central to adaptive immunity, orchestrating antigen-specific responses and maintaining long-term immunological memory [46]. During chronic inflammation, expansion of granulocytic myeloid-derived suppressor cells may impair lymphocyte proliferation and function, further skewing the immune profile toward an innate-dominant state and elevating the NLR

[39]. Higher NLR has been associated with increased risk of metabolic syndrome [36], type 2 diabetes [37], and cardiovascular disease [38], as well as with all-cause and cardiovascular mortality [39,40]. In SLGCI, NLR values, although elevated [41], typically remain below those seen in acute inflammation, where pronounced neutrophilia can raise the ratio substantially (i.e., ≥ 5) [49].

SLGCI is thought to be sustained by continuous exposure to both internal and external pro-inflammatory stimuli, including those derived from adipose tissue and diet [3,13,50].

Adipose tissue and systemic low-grade chronic inflammation

Body fat consists of lipids, primarily triglycerides, stored within adipocytes in adipose tissue [51]. Adiposity refers to the extent of fat storage [52], and when it exceeds thresholds such as those defined by body mass index (BMI) classifications, it is termed obesity [53]. Obesity is strongly associated with SLGCI [54–56]. This association is partly mediated by the immunometabolic activity of adipose tissue, which can be broadly categorized into subcutaneous and visceral depots [57]. Subcutaneous adipose tissue, located beneath the skin and distributed throughout the body, primarily serves as a long-term energy reservoir and provides thermal insulation and mechanical protection [57,58]. Visceral adipose tissue, in contrast, is located within the abdominal cavity, surrounding internal organs [57,58]. Although both depots function as energy stores, visceral adipose tissue is considered more metabolically active [59], partly due to its higher lipolytic activity [59,60].

As visceral adipose tissue expands in obesity, it may experience hypoxia due to insufficient vascularization [60], particularly since its angiogenic capacity is lower than that of subcutaneous adipose tissue [61]. Hypoxia, in turn, can induce oxidative stress, promote adipocyte fibrosis, and trigger cell death (e.g., necrosis), thereby upregulating inflammatory gene expression in tissue-resident immune cells [58,60,62], especially macrophages [63]. These pro-inflammatory macrophages secrete TNF-α, IL-6, and other mediators that contribute to local adipose tissue inflammation and promote SLGCI [58,60,64]. Consistent with this, observational studies have repeatedly reported a positive association between visceral adipose tissue area and circulating CRP concentrations [65–68].

Quantifying adipose tissue requires methods appropriate to the depot of interest. Subcutaneous and visceral adipose tissue volumes can be precisely measured using imaging techniques such as computed tomography or magnetic resonance imaging, which provide detailed assessments of regional fat distribution [58,69]. However, these methods are costly, time-consuming, and not routinely available in clinical or epidemiological settings [70]. Skinfold thickness, measured with calipers, offers a simpler and low-cost approach to estimating subcutaneous adipose tissue but is operator-dependent and less accurate [70]. Waist circumference, in turn, is a widely

used, cost-effective anthropometric measure of abdominal adiposity, a proxy for visceral adiposity [71–73], and has shown a consistent positive association with CRP in epidemiological studies [74–77], as well as with cardiometabolic disease [78–80].

Adipose tissue, leptin and adiponectin

Adipose tissue functions as an active endocrine organ, secreting a range of bioactive molecules known as adipokines, including leptin and adiponectin, which play important roles in energy metabolism and inflammation [81]. Leptin, primarily involved in the regulation of energy homeostasis, is secreted in direct proportion to adipose tissue mass [82–86]. Consequently, individuals with obesity generally exhibit elevated circulating leptin levels [82].

Preclinical studies have demonstrated that leptin acts as a chemoattractant for monocytes and macrophages, and enhances the production of pro-inflammatory cytokines, including IL-6, TNF-α, IL-1β, and IL-17, by immune cells expressing the leptin receptor, such as monocytes, macrophages, neutrophils, and $CD4^+$ T helper 17 cells [81,87]. Supporting this, observational studies have consistently reported positive associations between leptin levels and biomarkers of systemic inflammation, including total leukocyte count and CRP [88–92].

In contrast, adiponectin, which has insulin-sensitizing properties [81,93], is secreted in inverse proportion to adipose tissue mass [94,95], with markedly lower levels observed in individuals with obesity, particularly those with excess abdominal adiposity [94–100]. Beyond its metabolic role, preclinical studies have shown that adiponectin exerts anti-inflammatory effects through multiple mechanisms. Upon binding to its receptors (adiponectin receptors 1 and 2), it activates AMP-activated protein kinase and peroxisome proliferator-activated receptor alpha, leading to decreased activation of nuclear factor kappa B (NF-κB), a key transcription factor in inflammatory pathways [81,101]. Consequently, adiponectin suppresses the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while promoting the expression of anti-inflammatory cytokines including IL-10 in monocytes, macrophages, and regulatory T cells [81,93,101,102].

Observational studies have corroborated these mechanistic findings, reporting inverse associations between total adiponectin and inflammatory biomarkers such as NLR and CRP [103–107], as well as with the risk of type 2 diabetes [108,109] and cardiovascular disease [109–112]. However, larger studies and meta-analyses have questioned the predictive value of adiponectin for cardiovascular events [113–116], with some paradoxically reporting associations between higher adiponectin levels and increased cardiovascular and all-cause mortality [114,117], a phenomenon often referred to as the "adiponectin paradox" [118]. One potential explanation for this paradox lies in the existence of multiple adiponectin isoforms, namely, low-, medium-, and high-molecular-weight forms, which differ in their biological activity [102,119]. High-

molecular-weight adiponectin is considered the most biologically active isoform in terms of promoting insulin sensitivity and maintaining glucose homeostasis [120–122], whereas the low-molecular-weight form may exert more prominent anti-inflammatory effects [102]. Most large-scale studies, including those cited above, measured total adiponectin. This cannot distinguish isoforms and may partly explain inconsistent associations with disease outcomes. These inconsistencies further complicate efforts to interpret adiponectin's role in SLGCI and its contribution to cardiometabolic risk [102]. Investigating the interplay among adiposity, SLGCI, and cardiometabolic risk in populations that differ in lifestyle and metabolic health may help clarify adiponectin's physiological and pathological roles.

Overall, continuous exposure to pro-inflammatory stimuli originating from excess adipose tissue, such as hypoxia in expanding visceral depots and obesity-associated alterations in adipokines like leptin and adiponectin, may contribute to SLGCI [58,64,81]. Valuable insights into the relationship between excess adipose tissue, SLGCI, and cardiometabolic disease can be gained by assessing CRP and adiponectin concentrations in a lean traditional population with an apparent absence of cardiometabolic disease and comparing them with a control population from an industrialized society (Papers I and II).

Diet and systemic low-grade chronic inflammation

Excessive caloric intake and poor dietary quality contribute to the development of obesity [123], which, as discussed earlier, may sustain SLGCI through multiple pro-inflammatory stimuli. Beyond its role in driving adiposity, diet may also influence SLGCI through direct effects on the immune system. Accordingly, diets high in salt, sugar, refined cereal grains, hydrogenated fats, and ultra-processed foods have been associated with elevated levels of inflammatory biomarkers, including CRP [124] and NLR [125,126]. These dietary patterns may promote SLGCI by inducing gut microbiota dysbiosis with impaired intestinal barrier function, leading to endotoxemia, increasing oxidative stress, and contributing to the accumulation of advanced glycation end-products, all of which, together with other diet-sensitive pathways, prime NF-κB-dependent transcription and activate the NLRP3 inflammasome [3,127–129]. Conversely, diets rich in whole, minimally processed foods, such as fruits, vegetables, fatty fish, and nuts, have been associated with lower levels of inflammatory biomarkers [130–134]. These foods provide bioactive compounds, including micronutrients (e.g., magnesium, vitamin C), polyphenols, omega-3 fatty acids, and dietary fiber, which may support intestinal barrier integrity, reduce endotoxemia, mitigate oxidative stress, and inhibit pro-inflammatory pathways [135–142].

Among the dietary patterns studied for their anti-inflammatory potential, the Mediterranean diet and plant-based diets have been inversely associated with SLGCI biomarkers in observational and interventional studies [50,143–145]. Another

dietary pattern that has gained attention for its potential to reduce inflammation is the Paleolithic diet.

Paleolithic diet

Definition and rationale

Observations of contemporary hunter-gatherer populations, as well as traditional horticulturalists and other minimally industrialized groups, suggest that they exhibit lower adiposity, more favorable cardiometabolic biomarkers, and markedly lower prevalence of cardiometabolic diseases compared to populations in industrialized societies [146,147]. These populations primarily consume diets believed to resemble those of Late Paleolithic hunter-gatherers, raising the possibility that deviations from such dietary patterns in modern societies may contribute to the burden of chronic diseases [146–151]. This idea aligns with the evolutionary mismatch hypothesis, which postulates that the rapid transition from hunter-gatherer subsistence to agricultural and industrial food systems has outpaced human genetic adaptation, and may underlie the increased prevalence of chronic diseases [146–151].

Human ancestral subsistence strategies during the Paleolithic period, spanning approximately 3 million to 10,000 years ago [151–153], centered on hunting, fishing, and foraging [151]. Anatomically modern humans, who emerged around 300,000 years ago [154], followed dietary patterns shaped by ecological constraints, seasonal availability of resources, and food procurement strategies [149,151,155]. During the Late Paleolithic, the dietary pattern (henceforth referred to as the Paleolithic diet) included wild animals, fish, shellfish, larvae, insects, eggs, fruits, honey, vegetables, nuts, wild edible seeds (excluding those from the grass family), and tubers. It minimally incorporated foods introduced later through agriculture and industrialization, such as cereal grains, dairy products, legumes, ultra-processed foods, and added sugars and fats [149,151,155].

The notion that deviations from this ancestral diet may contribute to chronic disease is supported by both observational and interventional studies, which have suggested potential benefits of the Paleolithic diet in improving body composition and cardiometabolic health compared to contemporary diets [156–160]. To quantify how closely an individual's diet aligns with the Paleolithic model, the Paleolithic Diet Fraction (PDF) was developed [161]. PDF expresses the proportion of total daily intake (by weight or energy) derived from food groups considered Paleolithic. In randomized controlled trials (RCTs), a higher PDF has been associated with favorable metabolic outcomes, including reductions in body weight and waist circumference [161,162]. Furthermore, in the Malmö Diet and Cancer Study (MDCS), a large, population-based prospective cohort comprising more than 24,100 Swedish adults aged 44–74 years (63% women), a higher PDF was associated with a lower

incidence of cardiometabolic diseases and with reduced cardiovascular and all-cause mortality [156].

Paleolithic diet, abdominal adiposity, and systemic low-grade chronic inflammation

As previously discussed, excess adipose tissue, particularly visceral adiposity, is associated with SLGCI [65–68,74–76]. RCTs have shown that the Paleolithic diet results in greater reductions in measures of adiposity, such as body weight, BMI, and waist circumference, compared to other diets [158]. One proposed mechanism is the increased satiety induced by the Paleolithic diet [163,164], possibly due to the exclusion of cereal grains containing proteins like gluten and lectins, which have been hypothesized to promote leptin resistance [165,166]. Leptin resistance impairs satiety signaling and may promote overeating and body fat accumulation [167]. Supporting this hypothesis, an in vitro study showed that digested wheat gluten could inhibit leptin binding to its receptor [166]. However, a randomized cross-over trial in individuals with type 2 diabetes found no differences between a Paleolithic diet and a diabetes diet (which included cereal grains such as wheat, a source of gluten and lectins [165]) in total leptin, biologically active leptin (the receptor-bound fraction), or their ratio, likely because cooking abolishes this effect. Accordingly, the same study replicated the in vitro inhibition of leptin binding by digested gluten, but the effect disappeared after heat treatment [168].

Determining whether the exclusion of cereal grains plays a central role in mediating the adiposity-reducing effects of the Paleolithic diet, particularly with respect to visceral fat, could therefore be addressed through an intervention study that directly compares diets with and without cereal grains, using waist circumference (an accepted proxy for visceral adiposity [71,72]) as the primary outcome measure (Paper III). Beyond dietary factors, physical exercise has also been shown in clinical trials to reduce waist circumference [169] and lower inflammatory biomarkers such as CRP [170]. Although dietary interventions alone can significantly decrease waist circumference [158], the addition of long-term physical exercise may enhance these effects by further promoting fat mobilization and oxidation.

However, not all studies have found additional benefits from combining exercise and diet. For example, a short-term study in individuals with type 2 diabetes found no greater reduction in waist circumference when exercise was added to a Paleolithic diet compared to the diet alone [171]. Nevertheless, evidence from longer-term interventions suggests that the combination of diet and exercise may yield additive effects on waist circumference reduction compared to dietary changes alone [172]. To examine both the effect of cereal grain exclusion and the contribution of added long-term exercise, a factorial design could be employed, as implemented in Paper III. This approach enables the evaluation of both independent and

combined effects on waist circumference, helping to clarify whether cereal grain exclusion alone is sufficient to reduce visceral adiposity or whether additional benefits arise from its combination with sustained exercise.

Independent of adiposity, several characteristic components of the Paleolithic diet may exert anti-inflammatory effects that could further contribute to reduced SLGCI. The Paleolithic diet is rich in fruits, vegetables, nuts, and seeds (e.g., sunflower and pinyon seeds), which are high in fiber, polyphenols, and other phytochemicals that have been associated with reductions in inflammatory biomarkers such as CRP in both observational and interventional studies [130,134,173]. These compounds may also attenuate oxidative stress and downregulate the expression of pro-inflammatory genes [135], in addition to supporting gut barrier integrity [142]. Disruption of this barrier has been associated with increased translocation of lipopolysaccharide (LPS) from the gut lumen into the circulation [174], a phenomenon termed metabolic endotoxemia [175]. Elevated circulating LPS or its surrogate marker lipopolysaccharide-binding protein has been associated with SLGCI [176–178], in addition to obesity, type 2 diabetes, and cardiovascular disease [179–182]. Experimental human endotoxemia further supports this association: acute intravenous administration of LPS induces a transient but robust inflammatory response, with marked increases in cytokines such as TNF-α and IL-6, and impaired insulin sensitivity [183,184].

In addition, the Paleolithic diet is naturally abundant in essential micronutrients such as vitamin C, magnesium, and zinc [185,186]. These nutrients have been shown in RCTs to lower CRP concentrations [137,138,187], likely through mechanisms involving the mitigation of oxidative stress and the downregulation of pro-inflammatory transcription factors such as NF-κB [136,188,189]. When characterized by a high intake of omega-3 long-chain polyunsaturated fatty acids from fish and the exclusion of seed oils high in linoleic acid, the Paleolithic diet may also contribute to a more favorable omega-3 status [190,191]. Omega-3 fatty acids can influence inflammation by reducing the synthesis of pro-inflammatory eicosanoids and downregulating NF-κB activation, while also serving as precursors of specialized pro-resolving mediators that facilitate the resolution of inflammation [139,192,193].

Alongside these mechanisms, the exclusion of refined cereal grains and added sugars in the Paleolithic diet may further help prevent inflammatory responses. This is because such foods can induce postprandial hyperglycemia, which has been shown in human acute intervention studies to trigger oxidative stress and inflammatory activity in mononuclear cells [194,195]. Furthermore, this dietary pattern is generally lower in sodium than those typical of industrialized societies [196–199], largely due to the exclusion or limited intake of ultra-processed and packaged foods, as well as reduced use of added salt, both major sources of dietary sodium [200–202]. Given the potential pro-inflammatory effects of excessive sodium intake [203–205], its lower sodium content may reduce exposure to a dietary factor associated with inflammation and thereby contribute to the prevention or attenuation of SLGCI.

Since the Paleolithic diet excludes whole grains and dairy, it is important to briefly consider their relationship with inflammation. A systematic review and two meta-analyses of RCTs suggest that whole grains may modestly lower CRP, particularly in overweight or metabolically compromised individuals [206–208]. For dairy, systematic reviews and meta-analyses of RCTs consistently report neutral to beneficial effects on inflammatory biomarkers including CRP, with no evidence of pro-inflammatory effects [209–211].

In summary, the Paleolithic diet may prevent or decrease SLGCI not only by reducing adiposity but also by directly affecting the immune system, either through the inclusion of components with anti-inflammatory or pro-resolving properties or the exclusion of dietary factors that promote inflammation. This hypothesis is supported by animal research: in a long-term randomized intervention study in domestic pigs, a Paleolithic diet consisting of vegetables, fruits, meat, and tubers led to lower body weight, improved insulin sensitivity, reduced diastolic blood pressure, and CRP levels that were 82% lower compared with a cereal-based swine feed [212]. Further support comes from human studies, including a cross-sectional analysis showing that higher Paleolithic diet scores were associated with lower circulating CRP concentrations [213], and two systematic reviews and meta-analyses of RCTs demonstrating significant reductions in CRP following Paleolithic dietary interventions [159,160]. However, a recent umbrella review found no consistent association between Paleolithic diets and CRP [50], underscoring inconsistencies in the literature and highlighting the need for further research. Notably, while CRP is the most commonly assessed biomarker, other indicators of SLGCI such as total leukocyte count and NLR have yet to be evaluated in the context of Paleolithic dietary patterns. This represents an important knowledge gap and suggests the need to expand the range of inflammatory biomarkers under investigation.

The Malmö Diet and Cancer Study (MDCS), described above, provides a valuable opportunity to address this knowledge gap. This large population-based cohort study offers comprehensive dietary, anthropometric, and biomarker data. Within this cohort, elevated levels of SLGCI biomarkers, including total leukocyte count, NLR, and CRP, have been associated with increased risk of cardiometabolic diseases [29,30]. In parallel, analyses within the same cohort have shown that higher PDF is associated with a lower incidence of these conditions, as mentioned above [156].

If SLGCI acts as a mediator between a Paleolithic dietary pattern and reduced cardiometabolic disease risk, then PDF should be inversely associated with SLGCI biomarkers in this cohort. Accordingly, examining the relationship between PDF and inflammatory biomarkers in the MDCS (Paper IV) may provide important insights into the role of SLGCI in mediating the relationship between Paleolithic dietary patterns and cardiometabolic disease.

Aims

The general aim of this thesis is to investigate the relationship between the Paleolithic diet, abdominal adiposity, and SLGCI (Figure 1). Four studies employing both observational and interventional designs were conducted to explore different aspects of this relationship.

The specific aims of each paper are as follows:

1. **Paper I:** To assess serum CRP in a lean traditional population with minimal exposure to industrialized diet and lifestyle and an apparent absence of cardiometabolic disease, compared with an industrialized control population.
2. **Paper II:** To assess serum total adiponectin in the same two populations examined in Paper I.
3. **Paper III:** To assess the effects of a healthy diet excluding cereal grains versus one emphasizing whole grains, each with and without long-term physical exercise, on waist circumference.
4. **Paper IV:** To assess the association between PDF and inflammatory biomarkers (total leukocyte count, NLR, and CRP) in the Malmö Diet and Cancer Study (MDCS).

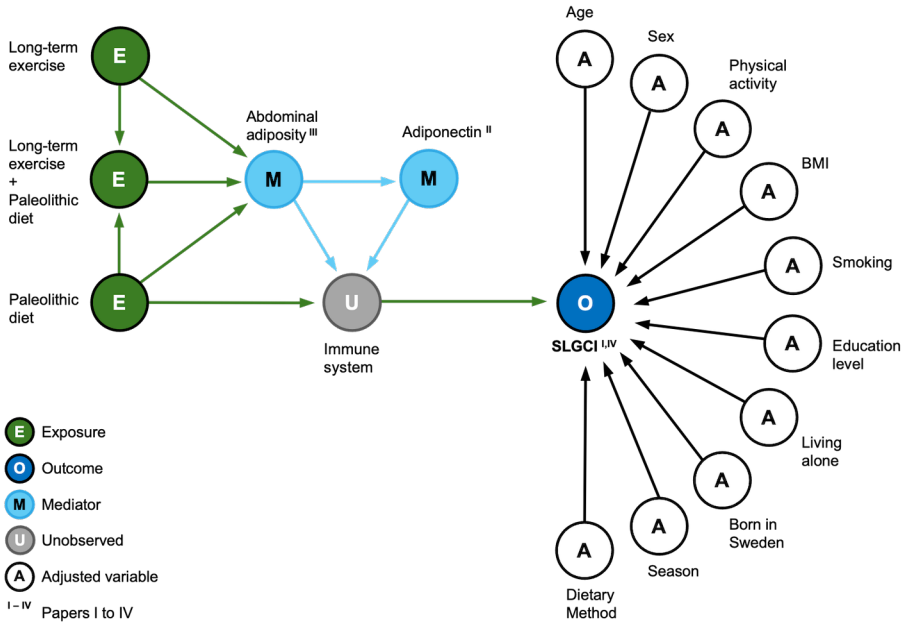

Figure 1. Graphical Representation of the Hypothesized Causal Framework for Papers I–IV
Note. Directed acyclic graph (adapted from DAGitty) depicting hypothesized causal pathways associating the Paleolithic diet and long-term exercise with systemic low-grade chronic inflammation (SLGCI), including direct effects of diet on the immune system (Papers I and IV) and indirect effects via abdominal adiposity (Paper III) and adiponectin (Paper II). Covariates included as adjustments in Paper IV analyses are also shown.
Abbreviations: A = adjusted variable; E = exposure; M = mediator; O = outcome; SLGCI = systemic low-grade chronic inflammation; U = unobserved.

Methods

Papers I and II

Design

Papers I and II are cross-sectional observational studies comparing serum CRP and total adiponectin, respectively, between indigenous Melanesians from Kitava, a remote island in the Trobriand Archipelago of Papua New Guinea, and age- and sex-matched Swedish controls. Kitavans represent a unique population minimally exposed to industrialized dietary and lifestyle patterns, with an apparent absence of obesity, type 2 diabetes, and cardiovascular disease [214–218].

Population

Kitavan population

Participants were part of the Kitava Study, a cross-sectional health investigation conducted in 1990 among indigenous Melanesians living on Kitava. The study included clinical examinations, interviews, anthropometric assessments, electrocardiograms, and fasting blood sampling [214]. The Kitavan lifestyle was based on subsistence horticulture and fishing. Their diet was composed primarily of fruits, tubers (yam, sweet potato, taro, and some cassava), fish, leafy vegetables, coconut, legumes, and nuts. It was virtually devoid of ultra-processed foods, added sugars, dairy products, and cereal grains (except small amounts of corn) [214]. Physical activity levels were classified as moderate-to-active, averaging 1.7 times basal metabolic rate [218]. Smoking and betel nut chewing were highly prevalent among adults [214,215].

All individuals aged > 50 years (N = 206) and a randomly selected 10% of those aged 40–50 years (n = 41) were eligible for participation. Due to a low venipuncture acceptance rate (41%), an additional 18 self-selected individuals aged 40–50 years were included, resulting in 110 Kitavans aged 40–86 years with fasting venous blood samples. CRP concentrations were ultimately available for 79 participants (Paper I) and total adiponectin for 102 participants (Paper II). Blood was collected in the morning following a minimum 9-hour fast without food, smoking, or betel

chewing. Samples were centrifuged within 3 hours, frozen within 1 hour, shipped to Sweden at −130 °C, and stored at −70 °C until analysis.

Swedish control population

Age- and sex-matched Swedish controls were randomly selected from the Skara Population Study, a population-based health survey conducted between 1993 and 1994 in Skara, Sweden [219]. This study was designed to be representative of the general Swedish population [219] and included participants aged ≥ 40 years who underwent comprehensive health examinations. Fasting venous blood samples were collected, centrifuged, and stored at −80 °C. Among the 110 Swedish controls selected for this study, CRP concentrations were available for 83 participants (Paper I) and total adiponectin for 108 participants (Paper II). Of these 110 controls, 12 had type 2 diabetes, 15 had hypertension, and 3 had both (n = 24 in total). Compared to national and local data from that period, the Swedish control sample showed a higher-than-expected prevalence of type 2 diabetes and a lower-than-expected prevalence of hypertension [219–223].

Outcomes

CRP (Paper I)

CRP was measured in serum using a high-sensitivity turbidimetric assay (Architect Ci8200 analyzer, Abbott Laboratories, USA). The lower limit of quantification was 0.20 mg/L, with a coefficient of variation of 4% at 1.4 mg/L. Values below the detection limit were imputed as 0.20 divided by the square root of 2, in accordance with assay specifications [224], affecting 14 Kitavans and 8 Swedish controls. Due to missing samples or insufficient volume, 58 samples were unavailable for analysis, leaving CRP data for 79 Kitavans and 83 Swedish controls. These comprised 59 matched pairs plus 20 Kitavans and 24 Swedish controls without matched counterparts. CRP values > 10 mg/L were retained for descriptive group comparisons but excluded from regression models, as such levels may reflect acute high-grade inflammation rather than SLGCI [20].

Total adiponectin (Paper II)

Total serum adiponectin was measured using a double-antibody radioimmunoassay (Linco Research, St Charles, MO, USA), employing rabbit anti-human adiponectin antibodies, ^{125}I-labeled human adiponectin as a tracer, and purified human adiponectin as standard. The coefficients of variation for inter- and intra-assay precision were 9.3% and 7.4%, respectively. Samples underwent a single freeze-thaw cycle to preserve analyte integrity. In total, 10 samples were missing, leaving adiponectin data for 102 Kitavans and 108 Swedish controls, including 100 matched pairs and an additional 2 Kitavans and 8 Swedish controls without matched counterparts.

Secondary outcomes

Both studies also analyzed lipid profiles (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, and triglycerides), anthropometric variables (body weight, BMI, waist and hip circumference, and waist-to-hip ratio), glycemic biomarkers (fasting glucose and insulin), and immune biomarkers (anti-phosphorylcholine [anti-PC] IgG and IgM antibodies).

Statistical analysis

All analyses were conducted using SPSS (version 28.0; IBM Corporation, Armonk, NY, USA). Statistical significance was set at $\alpha = .05$ (two-sided). Continuous variables were tested for normality and compared using independent *t*-tests when normally distributed or Mann-Whitney *U* tests when not. Categorical variables were compared using chi-square (χ^2) tests. For correlations, Pearson's *r* was used. When simple linear regression was not possible, the Spearman rank test was used.

For Paper I, CRP values > 10 mg/L were retained to characterize the full population distribution but excluded from regression analysis to avoid potential confounding by acute high-grade inflammation. To approximate normality and meet assumptions of parametric models, CRP was log-transformed (lnCRP) prior to correlation and regression analyses. Simple and multiple linear regression were used with lnCRP (for CRP < 10 mg/L) as the dependent variable.

For Paper II, total adiponectin was similarly log-transformed (lnadiponectin) to approximate a normal distribution and meet the assumptions of parametric analyses. One extreme outlier in each group (206 µg/mL in Kitavans and 104 µg/mL in Swedish controls) was winsorized to the next highest value to reduce skewness. Multivariable linear regression was used with total adiponectin as the dependent variable, adjusted for group, sex, smoking, hypertension and/or type 2 diabetes (categorical), age, and BMI (continuous). Among adiposity measures, only BMI was retained in the models because of strong collinearity ($r > .80$) with other anthropometric indicators. Interaction terms (e.g., age × sex, BMI × sex, age × BMI) were tested but none were statistically significant. All analyses were considered exploratory, no corrections for multiple testing were applied, and results should therefore be interpreted with caution.

Paper III

Design

Paper III is a 2-year RCT with a 2 × 2 factorial design, conducted at a public primary health care center in Lund, Sweden. The trial investigated the effects of dietary and physical activity interventions on waist circumference and related cardiometabolic risk factors in adults with increased waist circumference and at least one additional cardiovascular risk factor. Participants were allocated to five groups: (1) a healthy diet without cereal grains combined with exercise, (2) a healthy diet with whole grains combined with exercise, (3) a healthy diet without cereal grains and no exercise, (4) a healthy diet with whole grains and no exercise, and (5) a control group with follow-up only. Hereafter, "exercise" refers to an initial 8-week supervised group training program followed by long-term physical activity on prescription. The primary outcome was the change in waist circumference over 24 months. This factorial design enabled evaluation of both the independent and combined effects of cereal grain exclusion versus emphasis on whole grains, together with exercise.

Population

Eligible participants were recruited from patients attending the primary health care center and through local newspaper advertisements or leaflets in the waiting room. Inclusion criteria were a waist circumference of ≥ 84 cm in women or ≥ 98 cm in men and at least one of the following additional cardiovascular risk factors: history of coronary heart disease, stroke or transient ischemic attack, peripheral arterial disease, hypertension, type 2 diabetes, impaired glucose tolerance, prior gestational diabetes, smoking, or a first-degree relative with cardiovascular disease before 60 years of age or with type 2 diabetes. The thresholds for waist circumference were set midway between World Health Organization (WHO) "increased" and "substantially increased" cut-points [225] to capture individuals at elevated cardiometabolic risk while allowing a sufficient margin for clinically meaningful improvement. Specifically, they were chosen so waist circumference could decrease substantially during the study without falling below the WHO threshold for "increased risk" in Caucasians. Exclusion criteria included gluten sensitivity, severe obesity (i.e., BMI > 40 kg/m^2), age < 20 years, dependence on walking aids, difficulty understanding spoken or written Swedish, cognitive impairment; pronounced hearing loss, aphasia, and continuous treatment with anticoagulants or oral corticosteroids.

Between August 2010 and November 2014, a total of 86 individuals were assessed for eligibility. After screening, 73 participants (47 women and 26 men, aged 23–79

years) were enrolled and randomly allocated by computer to one of five groups in a factorial design (see CONSORT diagram, Figure 2).

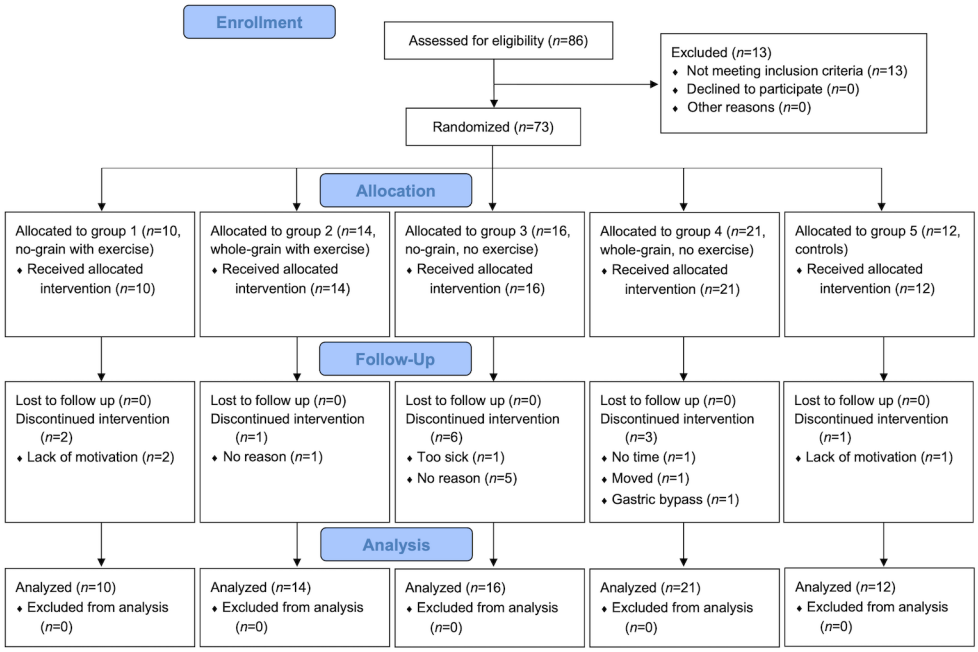

Figure 2. CONSORT Flow Diagram of Participant Progress Through the Study Phases

Interventions

Participants were randomly assigned to one of the following five groups: (1) diet without cereal grains plus exercise, (2) diet with whole grains plus exercise, (3) diet without cereal grains only, (4) diet with whole grains only, or (5) control (no structured intervention). Participants were followed for 24 months, with assessments conducted at baseline and at 3, 6, 12, and 24 months. The intervention structure, including the group allocation and schedule of measurements, is illustrated in Figure 3.

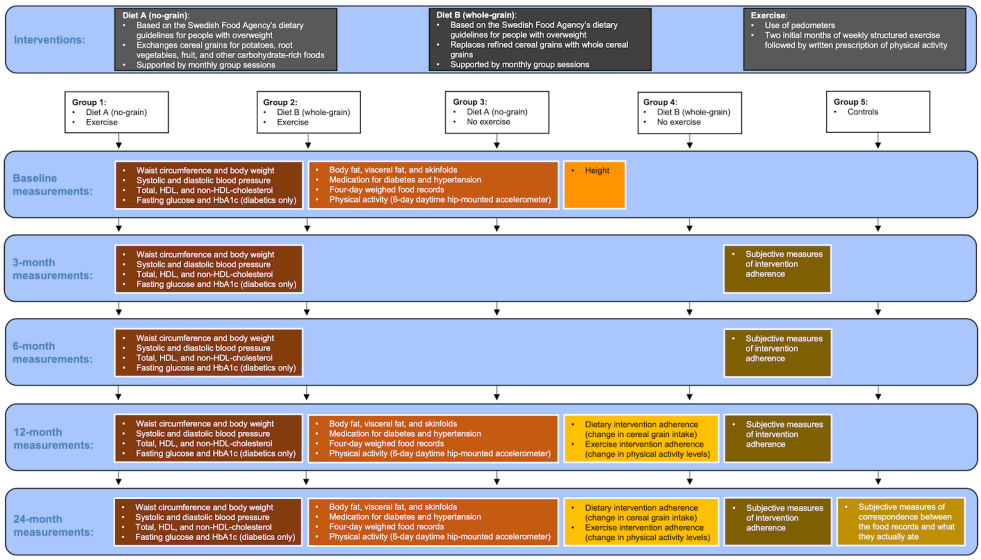

Figure 3. Overview of Study Design, Intervention Groups, and Assessment Timeline

All dietary interventions were based on the Swedish Food Agency's guidelines for individuals with overweight, emphasizing increased intake of fruits, vegetables, fish, lean meats, and low-fat dairy products, and discouraging candy, ice cream, snacks, cakes, pastries, chocolate, potato chips, beer, soft drinks, and juice. The two dietary approaches differed only in their recommendations regarding cereal-grain consumption.

The no-grain diet (Diet A) instructed participants to avoid all cereal grains, including bread, pasta, rice, breakfast cereals, porridge, and crackers, and instead consume carbohydrate-rich alternatives such as potatoes, root vegetables, fruits, corn, and legumes. The whole-grain diet (Diet B) encouraged participants to substitute refined grains with whole-grain options, including whole wheat bread, muesli, whole-grain pasta, and semolina, while aiming to maintain comparable carbohydrate intake across both dietary groups. Dietary advice was provided individually, both verbally and in writing, immediately after randomization. Participants were also invited to attend monthly group meetings (excluding July) during the intervention period to reinforce adherence and address questions.

In parallel, participants allocated to the exercise groups received pedometers and took part in supervised group training conducted by physiotherapists to enhance cardiorespiratory fitness: 2 sessions per week for 4 weeks, followed by 1 session per week for another 4 weeks. After this supervised phase, they received written prescriptions for continued individual physical activity and were encouraged to maintain regular exercise for the remainder of the study. Participants allocated to

the no-exercise groups were encouraged to follow national physical activity guidelines and received physical activity prescriptions as part of usual care.

Outcomes

The primary outcome was the change in waist circumference over 24 months. Secondary outcomes were changes in body fat, accelerometer-measured physical activity, blood pressure, non-HDL cholesterol, and changes in blood sugar-lowering medications; for participants with diabetes only, fasting blood glucose and glycated hemoglobin (HbA1c) were also secondary outcomes. Measurements were taken at baseline, 3, 6, 12, and 24 months, except for physical activity, dietary intake, body fat, subcutaneous fat, and medication use, which were assessed only at baseline, 12 months, and 24 months.

Statistical analysis

All analyses were performed using SPSS (version 28.0; IBM Corporation, Armonk, NY, USA). A pre-study power calculation indicated that enrolling 200 participants would provide 80% power to detect a between-group difference of 2 cm in waist circumference ($SD = 2.9$ cm), assuming $\alpha = .05$ (two-sided) and 20% attrition. Given the final sample size of 73, the trial was underpowered to detect small-to-moderate effects and should be interpreted accordingly.

Normality was assessed with Q-Q plots and the Shapiro-Wilk test. Primary analyses were conducted according to the intention-to-treat principle. Between-group comparisons were made using chi-square (χ^2), Fisher's exact, one-way ANOVA, or Kruskal-Wallis tests, as appropriate. Post hoc analyses were Bonferroni-adjusted (Tukey for ANOVA; Mann-Whitney U test for nonparametric comparisons).

Secondary analyses included mixed-effects models and ANCOVA to account for repeated measures and to adjust for covariates. Statistical significance was set at $p < .05$ for all tests.

Paper IV

Design

Paper IV is a cross-sectional analysis of the MDCS cohort in southern Sweden. It examines associations between PDF, a continuous variable representing the proportion of an individual's total food intake derived from food groups classified as Paleolithic, and circulating SLGCI biomarkers (total leukocyte count, NLR, and CRP).

Population

The MDCS recruited men (born 1923–1945) and women (born 1923–1950) residing in Malmö, Sweden, between 1991 and 1996 [226]. Of the 28,098 participants with complete baseline data [156], 23,250 individuals were included in the present analysis after excluding participants with a history of myocardial infarction, angina pectoris, stroke, or type 2 diabetes, individuals with high-grade inflammation (defined as total leukocyte count > 11×10^9/L or NLR ≥ 5), those with missing covariates, or those whose dietary data were insufficient to calculate PDF. Participants examined in 1991 were also excluded because the dietary data from that year did not support accurate PDF calculation [156].

CRP was measured in a subpopulation of individuals who were randomly selected to provide additional blood samples approximately 4 months after baseline assessment. Within this subpopulation, those with CRP > 10 mg/L were excluded due to the likelihood of acute high-grade inflammation [20]. This yielded a final analytic sample of 4,196 participants for CRP analysis. A detailed flowchart of the selection process for both analytic populations is presented in Figure 4.

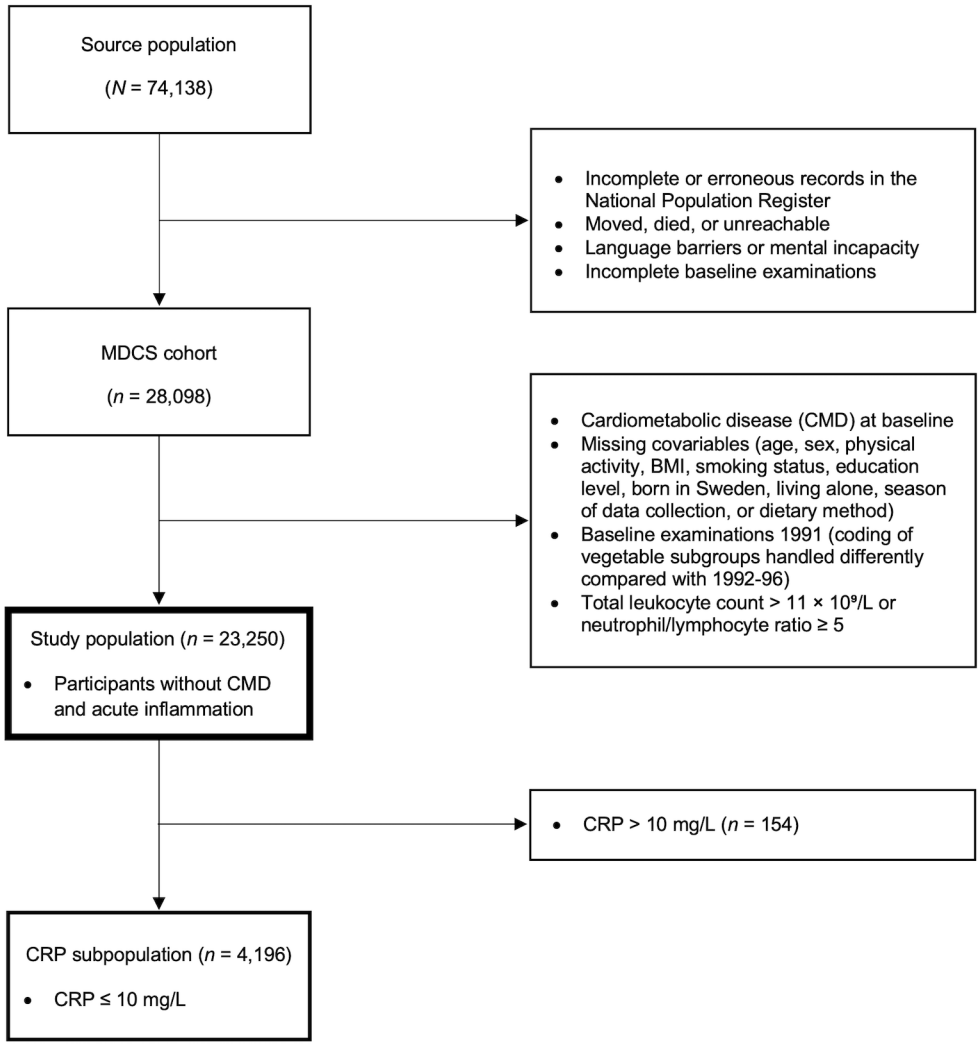

Figure 4. Flowchart of Participant Selection from the Malmö Diet and Cancer Study
Note. The study population and CRP subpopulation were comprised of participants from the MDCS without previous coronary events, diabetes, stroke, or high-grade inflammation, and with no missing covariate data at baseline (1992–1996).
Abbreviations: BMI = body mass index; CMD = cardiometabolic disease; CRP = C-reactive protein; MDCS = Malmö Diet and Cancer Study.

Dietary assessment and PDF calculation

Dietary intake at baseline was assessed using a validated modified diet history method that combined three components: a 7-day food diary (capturing variable meals, beverages, and supplements), a 168-item food frequency questionnaire, and

a 45-min interview conducted by trained dietitians. This multimodal approach enabled accurate estimation of habitual dietary patterns, portion sizes, and food group consumption [156,227,228]. Food items were coded and grouped using a database developed by the Swedish National Food Administration, supplemented with cohort-specific recipes [228].

To account for procedural changes introduced in September 1994, particularly affecting food coding and portion-size estimation, a binary variable was created to distinguish between dietary data collected before and after this revision [228].

PDF was calculated as the proportion (by weight) of daily food intake derived from food groups designated as Paleolithic: vegetables, fruits, potatoes, eggs, meat, fish, olive and rapeseed oil, nuts, and wine. Non-Paleolithic groups comprised legumes, juice, meat products, milk and milk products, sweet beverages, cereals (including rice), fats/oils and margarine, bakery sweets, jam, sauces and soups, beer, spirits, and miscellaneous items [156,161,162]. Non-caloric beverages such as water, tea, and coffee were excluded from the computation of PDF. This classification was informed by RCTs of the Paleolithic diet [198,229], studies that developed and applied PDF [161,162], and its prior operationalization in the MDCS cohort to study cardiometabolic morbidity and mortality [156]. Wine, although not part of a strict Paleolithic diet, was included in accordance with Paleolithic diet trial protocols that allowed moderate consumption [198,229]. Olive and rapeseed oil were also classified as Paleolithic because they were permitted in moderate amounts in those trials [198,229] and are rich in unsaturated fatty acids, paralleling ancestral fat sources such as nuts and the meat and bone marrow of wild animals [155,230,231]. Their inclusion is further supported by evidence of favorable cardiometabolic effects in observational and interventional studies [232,233] and by the Nordic Nutrition Recommendations 2023, which identify these oils as preferred sources of dietary fat [234]. Conversely, “fats/oils and margarine” in the non-Paleolithic category referred to refined oils (excluding olive and rapeseed), as well as added fats such as butter and margarines. For clarity, “meat” (classified as Paleolithic) denoted fresh, lean, unprocessed cuts of beef, pork, poultry, or game, whereas “meat products” (classified as non-Paleolithic) referred to processed meats such as sausages, spreads, or mixed offal preparations containing added salt, fat, or preservatives. This distinction is consistent with the definition used in a previous application of PDF [156]. Unlike studies using detailed weighed food records, where PDF could be derived from energy contributions [161,162], in the MDCS it was calculated only by weight due to database limitations, consistent with its prior use in this cohort [156].

Outcomes

Biomarkers of SLGCI were total leukocyte count, NLR, and CRP. Total leukocyte count and the leukocyte differential were measured at baseline in heparinized blood using the SYSMEX K1000 automated hematology analyzer (Sysmex Corporation).

NLR was calculated as absolute neutrophils divided by absolute lymphocytes. In a randomly selected subpopulation, fasting blood was collected approximately 4 months after baseline; plasma was stored at −80 °C and CRP was analyzed using a high-sensitivity latex-enhanced immunoassay (Tina-quant CRP, Roche Diagnostics). CRP values > 10 mg/L were excluded to reduce the influence of acute high-grade inflammatory responses [20].

Covariates

Covariates included age, sex, physical activity (sex-specific quintiles based on weighted weekly duration), BMI (categorized as underweight, normal weight, overweight, or obesity), smoking status (never, former, occasional, regular), education level (≤ 8, 9–10, 11–13 years, or university), living alone (yes or no), born in Sweden (yes or no), season of dietary data collection, and dietary method version (pre- vs. post-1994 revision).

These covariates were selected based on their established role as potential confounders in nutritional epidemiology [235] and prior evidence of their association with systemic inflammation [170,236–247]. For example, higher BMI, lower physical activity, or smoking habits are associated with elevated levels of inflammatory biomarkers, including CRP [237,241,242]. Similarly, education level and living alone have been associated with inflammation, potentially reflecting broader socioeconomic and psychosocial influences on health [243–246]. The covariate born in Sweden was included to account for potential ethnic or cultural differences in dietary habits that might influence both PDF and inflammation. Season of dietary collection was included due to known seasonal variation in food intake and availability, which may affect dietary exposure and associated nutrient intake. Additionally, the dietary method version variable was included to account for procedural changes implemented in September 1994, involving standardized coding of mixed dishes and revised portion-size estimation. Although validation studies have shown that these changes had minimal impact on participant rankings by dietary intake [228], they may still introduce subtle systematic differences.

Statistical analysis

Analyses were conducted using SPSS (version 29.0.2.0; IBM Corporation, Armonk, NY, USA). To meet model assumptions, CRP was log-transformed (lnCRP) before regression analyses. Associations between PDF and each inflammatory biomarker (total leukocyte count, NLR, and lnCRP) were evaluated using simple and multiple linear regression models. Two multivariable models were specified: an age- and sex-adjusted model and a fully adjusted model including all covariates listed above (age, sex, physical activity level, BMI, smoking status, education level, living alone, born in Sweden, season of dietary collection, and dietary method version).

Sensitivity analyses were stratified by sex, age tertiles, and PDF tertiles, and the corresponding interaction terms were tested. Exploratory linear regression models analogous to those for PDF examined individual food groups in relation to each biomarker. Correlations were assessed using Pearson's r or Spearman's r_s as appropriate. Correlations among inflammatory biomarkers are reported as Spearman's r_s. All tests were two-sided, with statistical significance set at $p < .05$.

Ethical considerations

Papers I and II

The Kitava study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethical Committee of the Medical Faculty at Lund University (LU 246-96), the Medical Research Advisory Committee of Papua New Guinea, other relevant national and provincial authorities, and the community leadership in Kitava. Because of high illiteracy rates among participants, informed consent was obtained verbally during interpreter-assisted reviews with the study physician and documented in the study protocol. Participants either signed or made a personal mark next to their printed name in the study protocol to confirm consent.

In Sweden, the analysis of stored blood samples from the Swedish controls was approved by the Ethics Committee of the Medical Faculty at Gothenburg University (GU 343-93). Here too, informed consent was obtained verbally during interviews with study personnel and documented in the protocol, in accordance with the informal procedures commonly used in community-based population studies at the time.

Paper III

The study protocol for the RCT was approved by the Regional Ethical Review Board in Lund, Sweden (LU 2010/332) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. Participants were informed of their right to withdraw from the study at any time without consequence. Data confidentiality and participant privacy were maintained throughout the trial.

Paper IV

The MDCS was approved by the Regional Ethics Review Board in Lund, Sweden (Dnr. LU51-90) and conducted in accordance with the Declaration of Helsinki. All

participants provided written informed consent prior to participation. Confidentiality and voluntary participation were ensured, and all participants were informed of their right to withdraw at any time without consequence. Data collection, handling, and storage procedures adhered to ethical guidelines designed to protect personal and health-related information.

Results

Overview

An overview of the studies included in this thesis is presented in Table 1.

Table 1
Overview of Studies Included in this Thesis

	Papers I and II	Paper III	Paper IV
Aims	To assess C-reactive protein (CRP) (Paper I) and total adiponectin (Paper II) levels in a lean, traditionally living Melanesian population (Kitavans) compared with an age- and sex-matched Swedish control group.	To test the effects of excluding cereal grains versus emphasizing whole grains, with or without long-term exercise, on waist circumference over 2 years.	To investigate the association between Paleolithic Diet Fraction (PDF) and biomarkers of systemic low-grade inflammation (total leukocyte count, neutrophil-to-lymphocyte ratio [NLR], and CRP) in the Malmö Diet and Cancer Study (MDCS) cohort.
Design	Cross-sectional observational study.	2-year randomized controlled trial with a 2 × 2 factorial design.	Cross-sectional analysis of a cohort study.
Population	Indigenous Melanesians from Kitava, Papua New Guinea, aged ≥ 40 years; CRP analysis (Paper I): *n* = 79 Kitavans, *n* = 83 Swedish controls; adiponectin analysis (Paper II): *n* = 102 Kitavans, *n* = 108 Swedish controls.	Adults aged 23–79 years (*n* = 73) with elevated waist circumference and ≥ 1 cardiometabolic risk factor.	MDCS participants aged 44–74 years; total sample: *N* = 23,250; CRP subsample: *n* = 4,196.
Intervention	None (observational).	Diet with or without cereal grains, with or without structured physical exercise, or control (usual care).	None (observational).
Outcomes	CRP (Paper I); total adiponectin (Paper II).	Primary: change in waist circumference over 24 months; secondary: metabolic, anthropometric, dietary, and lifestyle variables.	PDF (exposure); total leukocyte count, NLR, and CRP (outcomes).
Main results	Kitavans had significantly lower CRP and total adiponectin than Swedish controls, despite higher smoking and infection burden.	Greatest (but not significant) reduction in waist circumference observed in the no-grain, no-exercise group.	PDF was inversely and independently associated with total leukocyte count, NLR, and CRP.

Papers I and II

Sample characteristics and group differences

Participant characteristics for the Kitavan and Swedish control groups are shown in Tables 2.1 (Paper I) and 2.2 (Paper II). Both studies examined the same source populations, but the analyzed participants differed slightly between papers because of sample availability. Although group differences were examined across all measured variables, the primary outcomes differed: CRP in Paper I and total adiponectin in Paper II.

Kitavans exhibited significantly lower CRP levels compared to Swedish controls (median [*Mdn*] 0.5 mg/L, range 0.1–48 mg/L vs. *Mdn* 1.1 mg/L, range 0.1–33 mg/L; $r = .18$, $p = .02$). When limited to CRP < 10 mg/L, medians were 0.5 mg/L (0.1–8.2) for Kitavans and 1.0 mg/L (0.1–7.2) for controls. In a sensitivity analysis excluding Swedish controls with type 2 diabetes and/or hypertension ($n = 19$), the between-group difference for all CRP values was no longer significant ($p = .065$) but remained for CRP < 10 mg/L ($r = .18$, $p = .038$).

Total adiponectin concentrations were also significantly lower in Kitavans than in Swedish controls (*Mdn* 4.6 µg/mL, range 0.8–206 µg/mL vs. *Mdn* 9.7 µg/mL, range 3.1–104 µg/mL; $r = .64$, $p < .001$).

Among Kitavans, CRP levels did not differ between self-selected and randomly selected participants, as well as across sex and smoking status. Similarly, in Swedish controls, no significant differences were observed by sex, smoking status, or the presence of type 2 diabetes and/or hypertension.

To contextualize clinical relevance, participants were categorized using established CRP thresholds for cardiovascular risk and for distinguishing low-grade from high-grade inflammation [20]: < 1 mg/L (lower risk), 1–3 mg/L (average risk), 3–10 mg/L (higher risk), and > 10 mg/L (potential acute high-grade inflammation). As illustrated in Figure 5, Kitavans predominantly fell into the lower-risk category, whereas Swedish controls showed a broader distribution across risk strata, including a higher proportion with CRP > 3 mg/L.

CRP associations (Paper I)

Among Kitavans, lnCRP (restricted to CRP values < 10 mg/L) was inversely associated with total, LDL, and non-HDL cholesterol ($r = -.25$, $-.24$, and $-.23$; $B = -0.28$, -0.28, and -0.26; $p = .031$, $.045$, and $.050$, respectively), with no significant associations for triceps skinfold thickness or leptin.

Among Swedish controls, lnCRP (restricted to CRP values < 10 mg/L) was positively associated with weight (r = .40, B = 0.031), BMI (r = .47, B = 0.11), waist circumference (r = .46, B = 0.039), hip circumference (r = .40, B = 0.050), and waist-to-hip ratio (r = .31, B = 3.8). All associations were significant (p = .006 for waist-to-hip ratio and p < .001 for the others). Additional positive associations were found with triglycerides, the total cholesterol-to-HDL ratio, the triglyceride-to-HDL ratio, and serum insulin (with correlations ranging from r = .26 to .29, p < .05 for all).

In combined analyses of Kitavans and Swedish controls, lnCRP (restricted to CRP values < 10 mg/L) was positively associated with weight, BMI, and waist and hip circumference (with correlations ranging from r = .26 to .33, all $p \leq .002$). These anthropometric measures were highly intercorrelated (data not shown). Small positive associations were also found with fasting blood glucose (r_s = .22, p = .007) and with group (Kitavan vs. Swedish control; r = .18, B = 0.41, p = .029). However, in stepwise regression analysis including group, fasting blood glucose, and anthropometric indicators, only waist circumference remained a significant predictor of lnCRP, suggesting that group differences in CRP were largely explained by differences in abdominal adiposity.

CRP was not associated with anti-PC antibody levels in either group. Among Kitavans, those with positive serology for anti-centromere B antibodies (n = 4) had significantly higher CRP compared with seronegative participants (*Mdn* 3.1 vs. 0.4 mg/L, p = .02). No other autoantibodies or serologies were associated with CRP.

Adiponectin associations (Paper II)

Multivariable linear regression adjusting for group, sex, smoking, age, BMI, and hypertension and/or type 2 diabetes showed that belonging to the Kitavan group was strongly and significantly associated with lower total adiponectin in the combined-sample models (results available in Table 2 of Paper II).

Additional associations with lower total adiponectin included male sex (only among Swedish controls), smoking (in the combined sample only), younger age (not significant in Swedish controls), and higher BMI. In the combined sample, lower total adiponectin was also associated with lower total, LDL, and non-HDL cholesterol, and higher anti-PC IgG. An inverse association with HDL cholesterol was also observed, but only in the combined sample.

No significant associations were found with anti-PC IgM or IgA. No interaction terms (e.g., age × sex, BMI × sex, age × BMI) reached significance. Sensitivity analysis excluding all individuals with type 2 diabetes from the Swedish controls did not alter the findings. Figure 6A–C illustrates the relationship between total adiponectin and age, BMI, and LDL cholesterol, stratified by group.

Table 2.1
Baseline Clinical Characteristics of the Kitavan and Swedish Control Participants (Paper I – CRP Data)

Variable	Kitavans	Swedish controls	Effect size (*r*)
Sex (male / female), *n* (%)	61 (77%) / 18 (23%)	58 (70%) / 25 (30%)	
Smoking (yes / no), *n* (%)**	52 (69%) / 23 (31%)	20 (24%) / 63 (76%)	.45
Age, years *M* (*SD*)	58 (11)	60 (10)	
Weight, kg *M (SD)***	48 (8)	77 (13)	.83
Height, cm *M (SD)***	159 (7)	173 (9)	.65
Body mass index, kg/m^2 *M (SD)***	19 (2)	26 (4)	.78
Waist circumference, cm *M (SD)***	73 (5)	89 (12)	.73
Hip circumference, cm *M (SD)***	78 (5)	101 (8)	.86
Waist-hip ratio *M (SD)***	0.9 (0.0)	0.9 (0.1)	.30
Systolic blood pressure, mm Hg *M (SD)***	117 (17)	136 (19)	.47
Diastolic blood pressure, mm Hg *M (SD)***	70 (7)	77 (9)	.42
Fasting blood glucose, mmol/L *M (SD)***	3.8 (0.7)	5.1 (1.3)	.64
Fasting serum insulin, IU/mL *M (SD)***	4.7 (5.2)	6.2 (6.1)	.28
Total cholesterol, mmol/L *M (SD)***	5.0 (1.2)	5.7 (1.0)	.31
Triglycerides, mmol/L *M (SD)*	1.2 (0.5)	1.3 (0.8)	
HDL cholesterol, mmol/L *M (SD)**	1.0 (0.3)	1.2 (0.3)	.18
LDL cholesterol, mmol/L *M (SD)***	3.4 (1.1)	4.0 (0.9)	.33
Non-HDL cholesterol, mmol/L *M (SD)***	4.0 (1.1)	4.6 (0.9)	.28
Total-HDL cholesterol ratio, mol/mol *M* (*SD*)[a]	5.0 (1.4)	5.2 (1.4)	
LDL-HDL cholesterol ratio, mol/mol *M* (*SD*)[a]	3.4 (1.3)	3.6 (1.1)	
Triglyceride-HDL cholesterol ratio, mol/mol *M* (*SD*)[a]	1.3 (0.7)	1.3 (1.1)	
C-reactive protein, mg/L *Mdn* (range)*	0.47 (0.14–48)	1.10 (0.14–33)	.18
C-reactive protein < 10, mg/L *Mdn* (range)*	0.45 (0.14–8.2)	0.96 (0.14–7.2)	.21

Note. Clinical Characteristics and C-Reactive Protein of Kitavans and Swedish Controls with Samples Analyzed for C-Reactive Protein.
Normally distributed variables are presented as *M* (*SD*). Variables not normally distributed are presented as *Mdn* (Range).
p values: $p < .05$ (*) and $p < .001$ (**). [a] Values in mmol/L for ratios.
Abbreviations: LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Table 2.2
Baseline Clinical Characteristics of the Kitavan and Swedish Control Participants (Paper II – Adiponectin Data)

Variable	Kitavans	Swedish controls	Effect size (*r*)
Sex (male / female), *n* (%)	73 (72%) / 29 (28%)	76 (70%) /32 (30%)	
Smoking (yes / no), *n* (%)**	72 (74%) / 25 (26%)	26 (24%) / 82 (76%)	.50
Hypertension and/or type 2 diabetes (yes / no), *n* (%)**	0 (0%) / 102 (100%)	23 (21%) / 85 (79%)	.34
Age, years *M* (*SD*)	59.9 (11.1)	59.4 (10.4)	
Weight, kg *M (SD)***	47.6 (7.7)	77.5 (13.5)	.83
Height, cm *M (SD)***	158.1 (7.2)	172.9 (9.0)	.68
Body mass index, kg/m^2 *M (SD)***	18.9 (2.1)	25.9 (4.1)	.79
Waist circumference, cm *M (SD)***	72.6 (5.0)	89.8 (12.0)	.75
Hip circumference, cm *M (SD)***	78.7 (4.7)	101.6 (8.3)	.85
Waist-hip ratio *M (SD)***	0.9 (0.0)	0.9 (0.1)	.27
Systolic blood pressure, mm Hg *M (SD)***	118.5 (18.1)	135.3 (18.3)	.43
Diastolic blood pressure, mm Hg *M (SD)***	70.1 (7.1)	77.2 (9.3)	.40
Fasting blood glucose, mmol/L *M (SD)***	3.9 (0.7)	5.0 (1.2)	.63
Fasting serum insulin, IU/mL *M (SD)***	4.5 (4.8)	6.1 (5.7)	.31
HOMA-IR *M* (*SD*)**	0.8 (1.0)	1.5 (1.8)	.44
Total cholesterol, mmol/L *M (SD)***	5.1 (1.2)	5.8 (0.9)	.32
Triglycerides, mmol/L *M (SD)*	1.2 (0.5)	1.3 (0.7)	
HDL cholesterol, mmol/L *M (SD)**	1.1 (0.2)	1.1 (0.3)	
LDL cholesterol, mmol/L *M (SD)***	3.5 (1.1)	4.0 (0.9)	.32
Non-HDL cholesterol, mmol/L *M (SD)***	4.0 (1.1)	4.6 (0.9)	.30
Total-HDL cholesterol ratio, mol/mol *M* (*SD*)[a]	5.0 (1.4)	5.3 (1.3)	
LDL-HDL cholesterol ratio, mol/mol *M* (*SD*)[a]*	3.4 (1.3)	3.7 (1.1)	.15
Triglyceride-HDL cholesterol ratio, mol/mol *M* (*SD*)[a]	1.2 (0.6)	1.3 (1.0)	
C-reactive protein, mg/L *Mdn* (range)*	0.5 (0.1–48.0)	1.1 (0.1–33.0)	.18
C-reactive protein < 10, mg/L *Mdn* (range)*	0.5 (0.1–8.2)	1.0 (0.1–7.2)	.21

Anti-PC IgA, units *M* (*SD*)**	1512.3 (711.2)	742.3 (471.1)	.35
Anti-PC IgM, units *M* (*SD*)**	978.7 (283.6)	734.1 (289.0)	.41
Anti-PC IgG, units *M* (*SD*)**	1237.4 (274.6)	814.2 (312.2)	.59
Adiponectin, total, µg/mL *Mdn* (range)**	4.6 (0.8–206.0)	9.7 (3.1–104.0)	.64
Adiponectin, total, µg/mL *M* (SD)*	6.9 (20.0)	11.3 (10.1)	.14
Adiponectin, total, µg/mL *M* (*SD*)[b]*	5.0 (2.3)	10.6 (5.0)	.59

Note. Clinical Characteristics and Total Adiponectin of Kitavans and Swedish Controls with Samples Analyzed for Adiponectin.
Normally distributed variables are presented as *M* (*SD*). Variables not normally distributed are presented as *Mdn* (Range).
p values: $p < .05$ (*) and $p < .001$ (**). [a] Values in mmol/L for ratios. [b] One total adiponectin extreme outlier each for Kitavans (206 ng/mL) and Swedish controls (104 ng/mL) was winsorized and replaced with the next highest value.
Abbreviations: HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density lipoprotein; PC = phosphorylcholine.

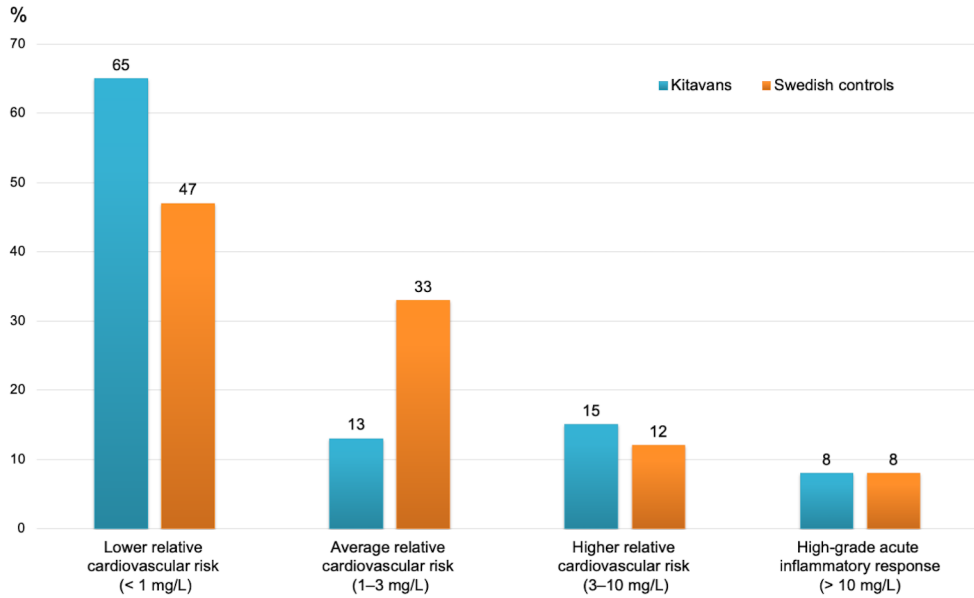

Figure 5. Distribution of C-Reactive Protein Categories in Kitavans and Swedish Controls
Note. Bars show the percentage (%) of Kitavans and Swedish controls within established C-reactive protein (CRP) categories [20]: < 1 mg/L (lower relative risk), 1–3 mg/L (average relative risk), 3–10 mg/L (higher relative risk), and > 10 mg/L (potential high-grade acute inflammatory response, e.g., infection or trauma).

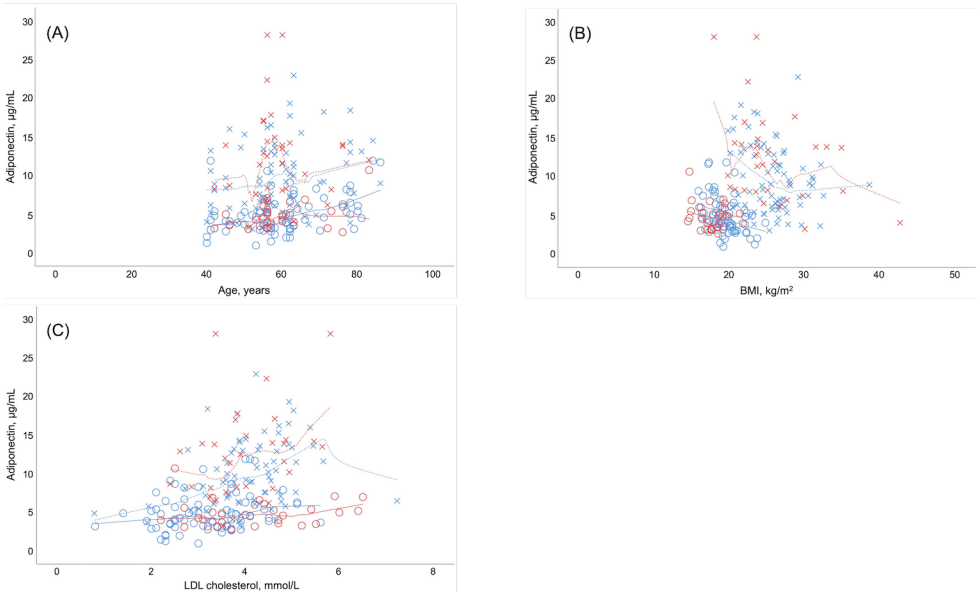

Figure 6A–C. Relationship between Total Adiponectin and Selected Associated Variables

Note. Circles (○) and solid lines denote Kitavans; crosses (X) and dashed lines denote Swedish controls. Lines are sex-specific locally weighted scatterplot smoothing (LOWESS) fits. Red denotes women and blue denotes men. One extreme total adiponectin value in each group (Kitavans 206 µg/mL; Swedish controls 104 µg/mL) was winsorized to the next highest value.
Abbreviations: BMI = body mass index; LDL = low-density lipoprotein.

Paper III

Seventy-three participants were randomized into five groups and included in the primary intention-to-treat analysis (Figure 2). Of these, 60 (37 women and 23 men) completed 24 months, while 13 discontinued, most commonly around 12 months. There were no significant between-group differences in baseline characteristics (Table 3.1) or in cardiovascular risk factors, medication use, or study discontinuation (results available in Table 2 of Paper III). No adverse events related to the interventions were reported.

Between-group comparisons showed no significant differences in change in waist circumference by diet or exercise allocation in the primary analyses (Table 3.2), and findings were consistent in secondary analyses, including per-protocol analyses and models adjusted for sex, age, and baseline body fat percentage. Summary statistics and secondary analyses are shown in Tables 3.2–3.5. Note that Table 3.5 reports only a subset of outcomes—whole-grain and cereal-grain intake and satiety measures (pre-meal rating, 30-min post-meal rating, intra-meal change, and satiety

quotient for energy) by group and time point. The complete dietary and satiety results are provided in Table 7 of Paper III.

The largest nominal between-group difference in waist circumference occurred at 12 months between the no-grain, no-exercise group (mean change = −5.3 cm; −4.7%, *SD* = 5.3) and the whole-grain, no-exercise group (mean change = −0.9 cm; −0.7%, *SD* = 5.4), a 4.4-cm (4.0%) difference that was not significant (95% CI [0.0%, 8.0%], $t(29) = -2.037$, $p = .051$, Cohen's $d = 0.75$; see Table 4 in Paper III).

Mixed models suggested a quadratic pattern in waist circumference, with greater reductions at 6 and 12 months and partial regain by 24 months across groups (Figure 7B). A between-group difference was detected only for the comparison of the no-grain plus exercise group with controls: the overall group contrast was significant ($p = .02$), and the simple comparison at 24 months showed less reduction in the no-grain plus exercise group than in controls ($p = .03$). No other significant between-group differences in trajectories were observed.

Dietary intake data corroborated adherence at 12 months: cereal-grain intake decreased in no-grain groups and increased in whole-grain groups (−43% vs. +28%, respectively, $p < .001$; Table 3.3 and Figure 7A), with no between-diet differences in total carbohydrate intake (Table 3.3). By 24 months, cereal-grain intake in the no-grain groups had risen and the between-group difference disappeared. The control group also reduced cereal-grain intake at 12 months (−9%) and more substantially by 24 months (−36%), despite receiving no structured dietary intervention. Notably, the control group showed numerically greater reductions in waist circumference than several intervention groups at some time points, though differences were not significant (Table 3.3).

Accelerometer-based physical activity showed no significant between-group differences in moderate-to-vigorous physical activity at any time point, including sensitivity analyses excluding participants with fewer than 6 valid days of accelerometer data (Table 3.4). At 12 months, the no-exercise groups showed the largest relative increase (+133%), followed by the exercise groups (+27%) and controls (+16%). By 24 months, however, physical activity levels had declined in all groups compared with 12 months, with the control group falling below baseline (Table 3.4 and Figure 7D).

Table 3.1
Baseline Characteristics

Variable	Group 1 Exercise Diet A (no-grain)	Group 2 Exercise Diet B (whole-grain)	Group 3 No-exercise Diet A (no-grain)	Group 4 No-exercise Diet B (whole-grain)	Group 5 Controls	One-way ANOVA *F* (4, 61–68[a])	η^2	*p*
Participants, *np*	10	14	16	21	12			
Male/female, *n*	3 / 7	2 / 12	6 / 10	10 / 11	5 / 7			.35
Age, years *M (SD)*	59 (11)	64 (5)	56 (13)	58 (12)	62 (8)	1.30	.07	.28
Height, cm *M (SD)*	168 (11)	169 (9)	170 (11)	174 (9)	169 (7)			.40
Waist circumference, cm *M (SD)*	109 (11)	106 (11)	110 (12)	106 (11)	108 (14)			.80
Weight, kg *M (SD)*	95 (16)	93 (14)	95 (14)	93 (14)	91 (17)	0.17	.01	.95
Body mass index, kg/m^2 *M (SD)*	33 (3)	33 (5)	33 (6)	31 (3)	31 (5)			.38
Systolic blood pressure, mm Hg *M (SD)*	136 (21)	154 (16)	139 (17)	146 (17)	143 (20)			.17
Diastolic blood pressure, mm Hg *M (SD)*	84 (13)	84 (9)	84 (13)	87 (8)	82 (7)			.70
Fasting plasma glucose, mmol/L *M (SD)*	8.3 (1.3)	7.6 (0.5)	7.5 (0.9)	8.8 (3.2)	8.8 (1.3)	0.47	.13	.76
HbA1c, mmol/mol *M (SD)*	50 (3)	42 (2)	54 (11)	50 (18)	49 (12)			.34
Total cholesterol, mmol/L *M (SD)*	4.9 (0.8)	5.3 (1.2)	5.2 (1.2)	5.5 (1.3)	5.0 (1.2)	0.68	.04	.61
HDL cholesterol, mmol/L *M (SD)*	1.2 (0.2)	1.6 (0.5)	1.2 (0.3)	1.2 (0.3)	1.3 (0.4)			.059
Non-HDL cholesterol, mmol/L *M (SD)*	3.8 (0.9)	3.8 (1.2)	4.0 (1.1)	4.3 (1.2)	3.7 (1.0)	0.87	.05	.48
Body fat, % *M (SD)*	43$_b$ (6)	43 (6)	36 (8)	35 (8)	36$_b$ (4)			.011
Visceral fat, % *M (SD)*	15 (5)	13 (3)	12 (4)	13 (4)	14 (6)	0.71	.05	.59
Biceps skinfold, mm *M (SD)*	20 (5)	21 (9)	16 (6)	16 (6)	18 (7)	1.69	.10	.163
Triceps skinfold, mm *M (SD)*	32 (5)	31 (9)	27 (12)	26 (9)	26 (9)	1.29	.08	.28
Subscapular skinfold, mm *M (SD)*	38 (11)	34 (8)	33 (11)	33 (9)	35 (5)			.31
Supra-iliac skinfold, mm *M (SD)*	31 (6)	27 (7)	27 (9)	26 (10)	27 (8)	0.52	.03	.72

Note. Values are *M* (*SD*) unless otherwise indicated. Rows sharing subscripts differ significantly. [a] *n* = 13 for fasting plasma glucose.
Abbreviations: HbA1c = glycated hemoglobin; HDL = high-density lipoprotein.

Table 3.2
Between-Group Differences in Percent Change in Waist Circumference from Baseline

		Group 1				Group 2				Group 3				Group 4			
		Diet A (no-grain) + exercise				Diet B (whole-grain) + exercise				Diet A (no-grain) + no-exercise				Diet B (whole-grain) + no-exercise			
			95% CI of the difference				95% CI of the difference				95% CI of the difference				95% CI of the difference		
Compared with Group	Time (months)	Mean Difference	Lower	Upper	*p*	Mean Difference	Lower	Upper	*p*	Mean Difference	Lower	Upper	*p*	Mean Difference	Lower	Upper	*p*
2	3	0.8%	−2.9%	4.5%	.66												
3	3	1.6%	−2.2%	5.3%	.39	0.8%	−2.7%	4.3%	.64								
4	3	−0.5%	−3.2%	2.3%	.72	−1.3%	−3.9%	1.4%	.33	−2.1%	−4.7%	0.6%	.122				
5 (controls)	3	−0.6%	−4.0%	2.7%	.70	−1.4%	−4.9%	2.0%	.40	−2.2%	−5.7%	1.3%	.20	−0.2%	−2.7%	2.4%	.90
2	6	0.8%			.31												
3	6	1.7%			.49	0.9%			.90								
4	6	−0.4%			.84	−1.2%			.30	−2.1%	−5.8%	1.6%	.26				
5 (controls)	6	1.4%			.40	0.6%			.32	−0.3%			.82	1.8%	−1.8%	5.5%	.34
2	12	0.5%			.41												
3	12	3.0%	−2.9%	8.9%	.30	2.5%			.64								
4	12	−1.0%	−6.1%	4.1%	.69	−1.5%			.084	−4.0%	−8.1%	0.0%	.051				
5 (controls)	12	1.9%	−3.7%	7.4%	.49	1.3%			.66	−1.2%	−5.3%	3.0%	.56	2.8%	−1.0%	6.7%	.139
2	24	3.2%	−3.1%	9.6%	.31												
3	24	4.4%	−1.5%	10.3%	.135	1.2%	−4.0%	6.3%	.65								
4	24	3.4%	−3.3%	10.0%	.31	0.1%	−5.3%	5.6%	.96	−1.0%	−6.7%	4.7%	.72				
5 (controls)	24	4.3%	−1.3%	9.9%	.123	1.1%	−3.9%	6.0%	.66	−0.1%	−4.4%	4.2%	.97	0.9%	−4.5%	6.3%	.73

Note. Entries are between-group differences in percent change in waist circumference from baseline at each time point. Mean difference is computed as (index group − comparator); negative values indicate a greater reduction in the index group.The greatest intervention group difference occurred at 12 months between Group 3 (M = −5.3 cm [−4.7%], SD = 5.3%) and Group 4 (M = −0.9 cm [−0.7%], SD = 5.4%) yielding a non-significant group difference (Δ = 4.4 cm [4.0%], 95% CI [0.0, 8.0], $t(29) = -2.037$, $p = .051$, Cohen's $d = 0.75$).

Table 3.3
Dietary Intervention Adherence and Change in Waist Circumference

Variable	Time (months)	Group 1+3 Diet A (no-grain) *M*	*(SD)*	Group 2+4 Diet B (whole-grain) *M*	*(SD)*	Group 5 Controls *M*	*(SD)*	One-way ANOVA *F* (2, 58–70)	η^2	*p*
Cereal-grain intake, g	0	249	(153)	185	(100)	243	(113)			.22
Cereal-grain intake: change from baseline, %	12	-43_a	(66)	28_a	(84)	−9	(59)			< .001
	24	−17	(55)	12	(96)	−36	(24)			.122
Whole-grain intake, g	0	40	(31)	36	(22)	35	(27)			.94
Whole-grain intake: change from baseline, %	12	-32_a	(96)	98_a	(201)	−17	(61)			< .001
	24	29	(96)	62	(155)	14	(103)			.56
Carbohydrate intake, g	0	207	(55)	198	(72)	226	(52)	0.78	.03	.46
Carbohydrate intake: change from baseline, %	12	−11	(38)	−5	(32)	−17	(15)			.38
	24	−8	(42)	−8	(37)	−22	(13)			.82
Waist circumference, cm	0	110	(11)	106	(10)	108	(14)	0.81	.02	.45
Waist circumference: change from baseline, %	3	−3.8	(4.3)	−2.8	(3.8)	−2.1	(3.3)	0.75	.02	.48
	6	−3.8	(6.2)	−2.8	(6.2)	−4.1	(3.3)			.96
	12	−3.4	(6.4)	−1.4	(6.8)	−3.6	(4.0)			.68
	24	0.3	(6.1)	−0.6	(7.3)	−1.6	(4.6)	0.28	.01	.76
Self-rated diet-intake correspondence, %	24	64	(35)	72	(28)	89	(11)			.160
Self-rated compliance, 0–10	0–3	7.8	(2.8)	7.0	(2.2)	5.7	(0.6)			.134
	3–6	7.2	(3.3)	6.3	(2.0)	6.0	(0.0)			.161
	6–12	5.3	(3.2)	5.7	(2.3)	6.3	(0.6)			.95
	12–24	3.8	(2.7)	5.6	(2.4)	6.3	(0.6)			.061

Note. Values are *M* (*SD*). Rows sharing subscripts differ significantly. Negative percentages denote decreases from baseline.

Table 3.4
Exercise Intervention Adherence and Change in Waist Circumference

		Group 1+2		Group 3+4		Group 5		One-way ANOVA		
	Time	Exercise		No exercise		Controls				
Variable	(months)	(months)	*(SD)*	*M*	*(SD)*	*M*	*(SD)*	*F* (2, 45–70)	η^2	*p*
SED, min/d	0	564	(75)	602	(91)	621	(56)	2.47	.07	.092
SED: change from baseline, %	12	−3	(13)	−3	(12)	−1	(10)	0.08	.00	.93
	24	0	(10)	2	(17)	−1	(9)	0.24	.01	.79
MVPA, min/d	0	23	(19)	27	(18)	29	(18)			.45
MVPA: change from baseline, %	12	27	(108)	133	(527)	16	(86)			.98
	12[a]			9	(88)					.86
	24	23	(100)	3	(102)	−22	(37)			.35
Waist circumference, cm	0	108	(11)	107	(11)	108	(14)			.84
Waist circumference: change from baseline, %	3	−3.3	(4.1)	−3.2	(3.9)	−2.1	(3.3)			.64
	6	−3.2	(7.3)	−3.2	(5.4)	−4.1	(3.3)			.86
	12	−2.0	(8.0)	−2.3	(5.6)	−3.6	(4.0)	0.23	.01	.80
	24	0.7	(6.8)	−1.0	(7.0)	−1.6	(4.6)	0.59	.02	.56
Self-rated compliance, 0–10	0–3	7.9	(1.9)	6.8	(2.7)	5.7	(0.6)			.100
	3–6	7.4	(1.8)	6.1	(2.9)	6.0	(0.0)			.28
	6–12	6.2	(2.2)	5.1	(2.8)	6.3	(0.6)			.45
	12–24	5.2	(2.0)	4.8	(3.1)	6.3	(0.6)			.70

Note. Values are *M* (*SD*). Negative percentages denote decreases from baseline. [a] Analysis without two extreme outliers in Group 3.
Abbreviations: SED = sedentary time; MVPA = moderate-to-vigorous physical activity.

Table 3.5
Whole- and Cereal-Grain Intake and Satiety Measures by Group and Time Point

Variable	Time (months)	Group 1+3 Diet A (no-grain)		Group 2+4 Diet B (whole-grain)		Group 5 Controls		One-way ANOVA		
		M	*(SD)*	*M*	*(SD)*	*M*	*(SD)*	*F* (2, 54–61)	η^2	*p*
Whole-grain intake, g *M (SD)*	0	40	(31)	36	(22)	35	(27)			.94
	12	21_a	(27)	52_a	(35)	30	(26)			.002
	24	29	(15)	43	(32)	36	(38)			.29
Cereal-grain intake, g *M (SD)*	0	249	(153)	185	(100)	243	(113)			.22
	12	135	(126)	193	(104)	185	(89)			.163
	24	199	(163)	162	(71)	152	(97)			.63
Satiety before meal, RS *M (SD)*	0	−1.1	(0.5)	−1.1	(0.5)	−1.1	(0.5)	0.10	.00	.90
	12	−1.1	(0.6)	−1.0	(0.4)	−1.3	(0.5)	1.29	.04	.28
	24	−1.2	(0.5)	−1.0	(0.5)	−1.2	(0.4)	1.71	.06	.191
Satiety 30 minutes after meal start, RS *M (SD)*	0	1.4	(0.5)	1.4	(0.5)	1.3	(0.5)	0.14	.00	.87
	12	1.4	(0.6)	1.4	(0.5)	1.3	(0.6)			.55
	24	1.4	(0.6)	1.3	(0.5)	1.2	(0.4)			.51
Change in satiety during meal, RS *M (SD)*	0	2.5	(0.8)	2.4	(0.8)	2.4	(0.8)			.81
	12	2.4	(1.0)	2.5	(0.8)	2.7	(0.9)			.85
	24	2.7	(1.0)	2.3	(0.9)	2.4	(0.6)			.55
Satiety quotient for energy, RS/MJ *M (SD)*	0	2.6	(1.8)	3.5	(4.7)	2.1	(1.6)			.70
	12	2.8	(3.2)	3.6	(7.0)	1.8	(0.9)			.66
	24	2.1	(1.0)	2.0	(1.4)	1.7	(0.7)			.52

Note. Values are *M* (*SD*).
Abbreviations: RS = rating scale units.

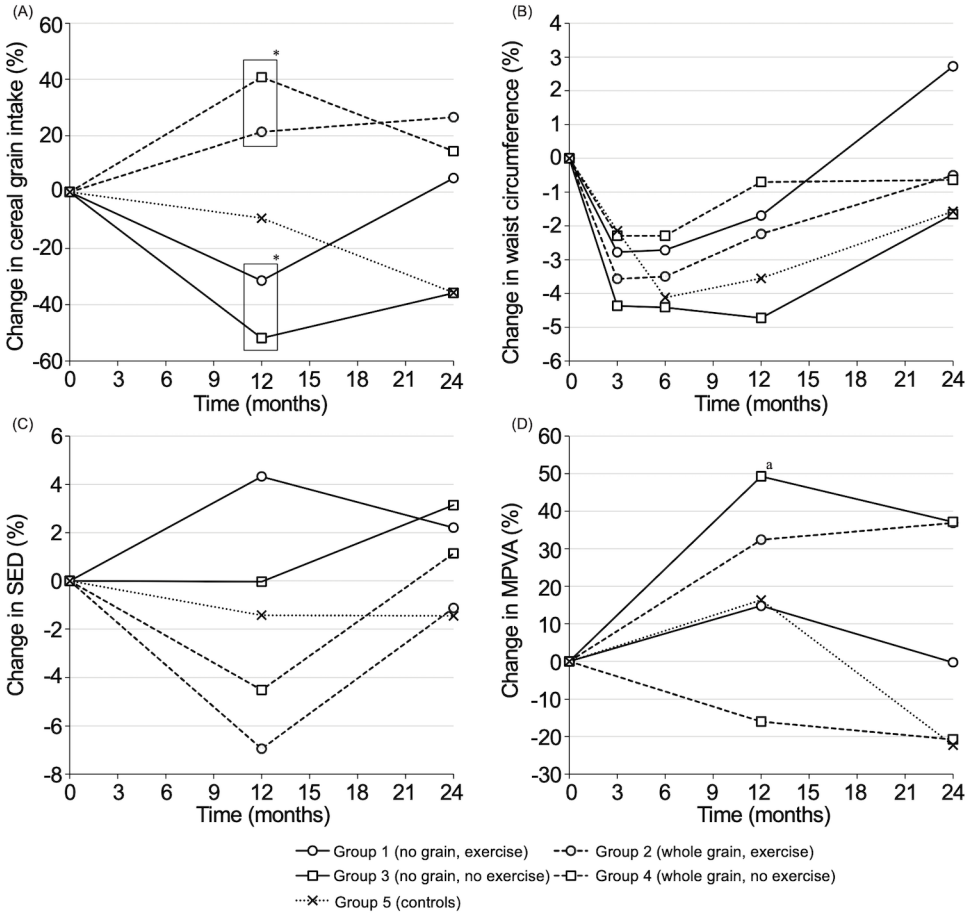

Figure 7. Changes in Intervention Adherence and Waist Circumference Over Time
Note. Panel A: Cereal-grain intake (% change). Panel B: Waist circumference (% change). Panel C: Sedentary time (% change). Panel D: Moderate-to-vigorous physical activity (% change). Error bars omitted for clarity.* Difference in pooled means between Groups 1+3 (no-grain) and 2+4 (whole-grain) at 12 months, $p < .001$. [a] Panel D values computed without two extreme outliers in Group 3. Abbreviations: MVPA = moderate-to-vigorous physical activity; SED = sedentary time.

Paper IV

Baseline characteristics of the study population (N = 23,250) and the CRP subpopulation (n = 4,196) are presented in Table 4.1. The mean PDF was 41% in the full population and 42% in the CRP subpopulation. Mean total leukocyte count was 6.3×10^9/L in the full population and 5.9×10^9/L in the subpopulation, the mean

NLR was 2.1 in both groups, and the mean CRP concentration in the subpopulation was 1.9 mg/L. Baseline daily intake of food groups is summarized in Table 4.2.

All three inflammatory biomarkers (total leukocyte count, NLR, and CRP) were weakly but significantly correlated. Spearman's correlation coefficients were r_s = .263 (total leukocyte count with NLR), r_s = .262 (total leukocyte count with CRP), and r_s = .062 (NLR with CRP), all $p < .001$.

PDF was significantly and inversely associated with all three inflammatory biomarkers in both unadjusted and multivariable-adjusted models (Table 4.3). In the fully adjusted model, higher PDF was associated with lower total leukocyte count ($B = -0.008$), lower NLR ($B = -0.003$), and lower lnCRP ($B = -0.005$), all $p < .001$. The fully adjusted model included age, sex, physical activity level, BMI, smoking status, education level, living alone, born in Sweden, season of dietary data collection, and dietary method version. Findings are illustrated in Figures 8–10. Sensitivity analyses stratified by sex and by tertiles of age and PDF showed broadly similar inverse associations across strata, with the exception of a significant PDF × age interaction for NLR (results available in Table S1 of Paper IV). In exploratory analysis, inverse associations were observed for Paleolithic food groups such as vegetables, fruits, and fish, and positive associations for non-Paleolithic groups, specifically meat products and milk and milk products, consistent with the overall PDF pattern (results available in Table S2 of Paper IV).

Table 4.1
Baseline Characteristics of the Study Population and the CRP Subpopulation

		Study population							CRP subpopulation						
Variables		***M***	***SD***	***Mdn***	***Min***	***Max***	***n***	**%**	***M***	***SD***	***Mdn***	***Min***	***Max***	***n***	**%**
Age (years)		57.9	7.7	57.3	44.5	73.6	23,250	100	57.4	6.0	57.7	46.0	68.0	4,196	100
Sex	Male						8,669	37						1,652	39
	Female						14,581	63						2,544	61
Height, cm		168.5	8.8	168.0	127.	203.0	23,250	100	168.9	8.8	168.0	144.0	201.0	4,196	100
Weight, kg		72.9	13.4	72.0	31.0	170.0	23,250	100	72.9	13.1	72.0	39.0	150.0	4,196	100
Body mass index, kg/m^2		25.6	3.9	25.2	13.9	50.9	23,250	100	25.5	3.8	25.0	15.6	50.7	4,196	100
Waist circumference, cm		83.2	12.6	82.0	50.0	152.0	23,250	100	82.7	12.4	82.0	54.0	152.0	4,196	100
Systolic blood pressure, mm Hg		140.8	19.9	140.0	61.0	230.0	23,250	100	140.7	18.7	140.0	94.0	210.0	4,196	100
Diastolic blood pressure, mm Hg		85.3	10.0	85.0	40.0	136.0	23,250	100	86.7	9.3	86.0	58.0	130.0	4,196	100
Physical activity score		8,221	6,774	6,888	0	316,120	23,250	100	8,314	5,913	7,124	0	48,900	4,196	100
Smoking status	Regular smoker						5,460	23						906	22
	Occasional smoker						1,050	5						194	5
	Stopped smoking						7,763	33						1,372	33
	Never smoked						8,977	39						1,724	41
Education level	< 9 years						9,440	41						1,879	45
	9–10 years						6,173	27						1,096	26
	11–13 years						4,188	18						696	17
	University degree						3,449	15						525	13
Living alone	No						17,598	76						3,257	78
	Yes						5,652	24						939	22
Born in Sweden	Yes						20,478	88						3,755	89
	No						2,772	12						441	11

Paleolithic Diet Fraction, %	41	11	40	0	90	23,250	100	42	11	41	7	88	4,196	100
Total leukocyte count, × 10^9/L	6.3	1.5	6.0	1.6	11.0	23,250	100	5.9	1.5	5.7	2.3	11.0	4,196	100
Neutrophil count, × 10^9/L	3.8	1.2	3.6	0.2	8.7	23,250	100	3.6	1.1	3.5	0.6	8.6	4,196	100
Lymphocyte count, × 10^9/L	1.9	0.6	1.9	0.5	6.0	23,250	100	1.8	0.5	1.8	0.5	5.6	4,196	100
Neutrophil/lymphocyte ratio	2.1	0.7	2.0	0.2	4.9	23,250	100	2.1	0.7	1.9	0.3	4.9	4,196	100
C-reactive protein, mg/L								1.9	1.8	1.2	0.1	10.0	4,196	100
Total cholesterol, mmol/L								6.2	1.1	6.1	3.0	11.8	4,196	100
LDL-c, mmol/L								4.2	1.0	4.1	1.0	9.8	4,196	100
HDL-c, mmol/L								1.4	0.4	1.4	0.5	3.1	4,196	100
Triglycerides, mmol/L								1.3	0.8	1.1	0.3	16.3	4,196	100
Total cholesterol/HDL-c ratio								4.7	1.4	4.5	1.9	13.0	4,196	100
LDL-c/HDL-c ratio								3.2	1.2	3.1	0.6	9.6	4,196	100
Triglyceride/HDL-c ratio								1.1	0.8	0.8	0.2	6.8	4,196	100
HbA1c, %								4.8	0.5	4.8	3.3	8.9	4,196	100
Fasting glucose, mmol/L								5.0	0.6	4.9	3.3	13.5	4,196	100
Fasting insulin, mIU								7.6	8.0	6.0	2.9	224.0	4,196	100
HOMA-IR								1.8	2.6	1.4	0.4	88.3	4,196	100

Note. Baseline clinical characteristics of the study population and the CRP subpopulation, both comprising MDCS participants without previous coronary events, diabetes, stroke, or high-grade inflammation, and with no missing covariate data at baseline (1992–1996). Continuous variables are presented as *M* (*SD*) and, where reported, median (*Mdn*), minimum (*Min*), and maximum (*Max*); categorical variables are *n* (%).
Abbreviations: BMI = body mass index; CRP = C-reactive protein; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; MDCS = Malmö Diet and Cancer Study.

Table 4.2
Daily Food Intake

Dietary and nutritional variables	Study population				CRP subpopulation			
	Mdn	*Min*	*Max*	*IQR*	*Mdn*	*Min*	*Max*	*IQR*
Paleolithic diet fraction, %	40	0	90	15	41	7	88	15
Total food group weight, g	1689	330	5242	620	1735	488	4371	629
Total food group energy, kcal	2180	516	8396	798	2224	627	5879	825
Total food group energy per gram, kcal	1	0.5	3	0.3	1	0.6	2	0.3
Paleolithic food groups, g	668	0	4089	290	700	138	2060	294
Vegetables, g	146	0	1177	110	162	1	933	119
Fruits, g	168	0	2782	152	182	0	1312	153
Potatoes, g	109	0	1447	84	110	0	862	91
Eggs, g	19	0	245	22	19	0	173	22
Meat[a], g	94	0	593	60	96	0	470	62
Fish, g	39	0	527	41	40	0	505	41
Rape seed and olive oil, g	0	0	74	0	0	0	26	0
Nuts, g	0	0	147	2	0	0	75	2
Wine, g	21	0	1127	71	21	0	764	71
Non-Paleolithic food groups, g	999	75	4182	512	1011	129	3417	513
Legumes, g	0	0	520	14	0	0	206	18
Juice, g	1	0	1371	100	1	0	1371	100
Meat products[b], g	24	0	341	35	25	0	293	37
Milk and milk products, g	395	0	3339	315	406	0	2200	315
Sweet beverages, g	9	0	3000	94	6	0	1714	86
Cereal grains (including rice), g	132	0	1114	81	139	1	1114	88
Fats, Oils, and Margarines, g	30	0	209	31	32	0	205	33
Bakery sweets, g	65	0	715	57	66	0	715	58
Jam, g	12	0	205	20	13	0	205	21
Sauce soups, g	3	0	1000	10	3	0	361	10
Beer, g	83	0	3143	193	86	0	1961	190
Spirits, g	0	0	550	7	0	0	236	7
Remainder miscellaneous, g	4	0	692	4	4	0	131	4

Note. Daily food-group intake in the study population and the CRP subpopulation, both comprising MDCS participants without previous coronary events, diabetes, stroke, or high-grade inflammation and with no missing covariate data at baseline (1992–1996). Values are median (*Mdn*), minimum (*Min*), maximum (*Max*), and interquartile range (*IQR*). Non-energy-containing beverages were excluded.
[a] Pork, beef, lamb, game meat, poultry, and pure offal. [b] Offal in mixed products, spreads, or sausages.
Abbreviations: CRP = C-reactive protein; MDCS = Malmö Diet and Cancer Study.

Table 4.3
Associations Between Paleolithic Diet Fraction and Inflammatory Biomarkers

Biomarker	Model	*n*	*B* for constant	*B*	*SE* Coeff	ß	*t*	*p*	Adj R^2 for model
Total leukocyte count, × 10^9/L		23,250							
	Non-adjusted		6.749	−0.012	.001	−0.090	−13.757	< .001	.008
	Age and sex adjusted			−0.013	.001	−0.100	−14.895	< .001	.010
	Fully adjusted*			−0.008	.001	−0.063	−10.037	< .001	.158
Neutrophil / lymphocyte ratio		23,250							
	Non-adjusted		2.272	−0.005	.000	−0.075	−11.409	< .001	.006
	Age and sex adjusted			−0.004	.000	−0.060	−8.924	< .001	.010
	Fully adjusted*			−0.003	.000	−0.048	−7.131	< .001	.019
Ln C-reactive protein		4,196							
	Non-adjusted		0.395	−0.005	.001	−0.057	−3.675	< .001	.003
	Age and sex adjusted			−0.005	.001	−0.060	−3.790	< .001	.012
	Fully adjusted*			−0.005	.001	−0.054	−3.555	< .001	.114

Note. Associations between Paleolithic Diet Fraction (%) and inflammatory biomarkers were assessed using simple and multivariable linear regression models. The study population and the CRP subpopulation both comprised MDCS participants without previous coronary events, diabetes, stroke, or high-grade inflammation and with no missing covariate data at baseline (1992–1996). *Adjusted for age, sex, physical activity level, body mass index, smoking status, education level, living alone, born in Sweden, season of dietary data collection, and dietary method version. CRP was log-transformed for analysis. Abbreviations: CRP = C-reactive protein; MDCS = Malmö Diet and Cancer Study.

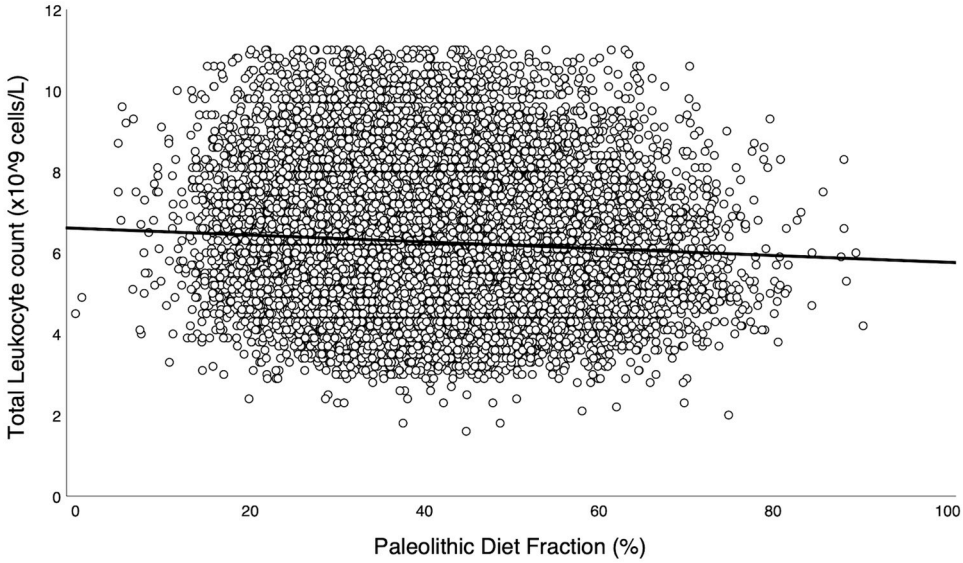

Figure 8. Association Between Paleolithic Diet Fraction and Total Leukocyte Count
Note. Association between Paleolithic Diet Fraction (PDF) and total leukocyte count in the study population (N = 23,250) comprised of participants from the Malmö Diet and Cancer Study (MDCS) without previous coronary events, diabetes, stroke, or high-grade inflammation, and with no missing covariate data at baseline (1992–96). The solid line depicts the fully adjusted linear regression fit (y = 6.603 − 0.008 × x, p < .001).
Abbreviations: MDCS = Malmö Diet and Cancer Study; PDF = Paleolithic Diet Fraction.

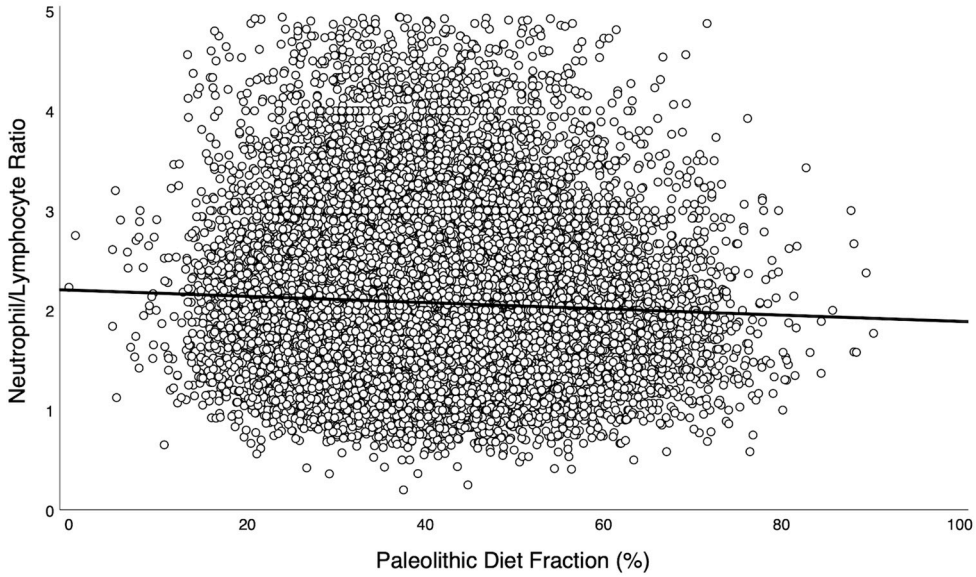

Figure 9. Association Between Paleolithic Diet Fraction and Neutrophil-to-Lymphocyte Ratio
Note. Association between Paleolithic Diet Fraction (PDF) and neutrophil-to-lymphocyte ratio in the study population (N = 23,250) comprised of participants from the Malmö Diet and Cancer Study (MDCS) without previous coronary events, diabetes, stroke, or high-grade inflammation, and with no missing covariate data at baseline (1992–96). The solid line depicts the fully adjusted linear regression fit ($y = 2.203 - 0.003 \times x$, $p < .001$).
Abbreviations: MDCS = Malmö Diet and Cancer Study; PDF = Paleolithic Diet Fraction.

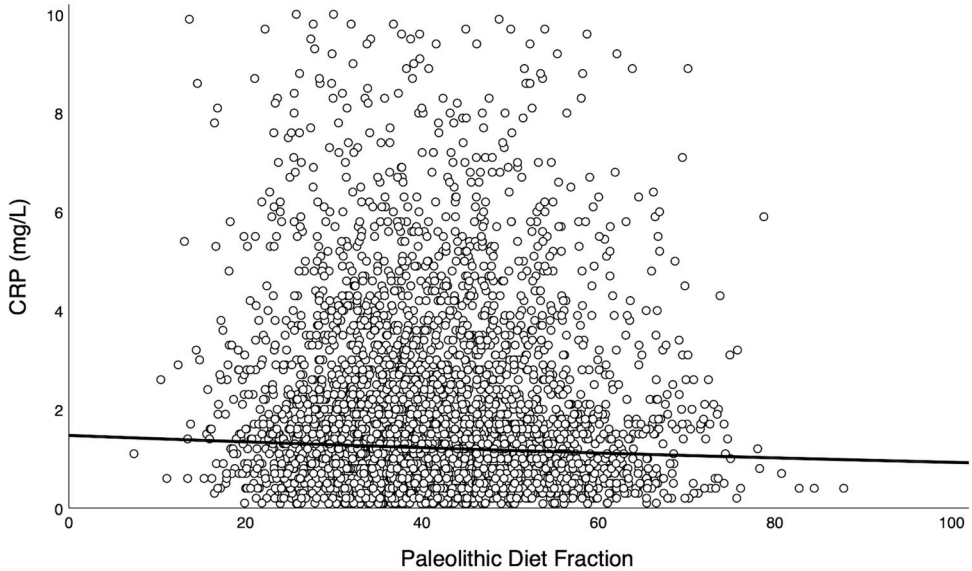

Figure 10. Association Between Paleolithic Diet Fraction and C-Reactive Protein

Note. Association between Paleolithic Diet Fraction (PDF) and C-reactive protein (CRP) in the CRP subpopulation (n = 4,196) comprised of participants from the Malmö Diet and Cancer Study (MDCS) without previous coronary events, diabetes, stroke, or high-grade inflammation, and with no missing covariate data at baseline (1992–96). The solid line depicts the fully adjusted regression fit, back-transformed from the natural logarithm of CRP [$y = \exp(-0.385 - 0.005 \times x)$, $p < .001$].
Abbreviations: CRP = C-reactive protein; MDCS = Malmö Diet and Cancer Study; PDF = Paleolithic Diet Fraction.

Discussion

The general aim of this thesis was to investigate the relationship between the Paleolithic diet, abdominal adiposity, and SLGCI (Figure 1). To address this aim, four studies employing complementary designs were conducted: two cross-sectional comparisons of a traditional and an industrialized population (Papers I and II), a long-term intervention trial (Paper III), and a cross-sectional analysis of a large-scale cohort study (Paper IV).

Main findings

Papers I and II

Paper I showed that Kitavans had significantly lower CRP concentrations than age- and sex-matched Swedish controls, despite a high prevalence of smoking and a considerable infectious burden in the former, two factors generally associated with elevated biomarkers of systemic inflammation, including CRP [242,248]. These findings suggest that SLGCI in Kitavans remains low even in the presence of such pro-inflammatory exposures, likely reflecting protective influences such as low adiposity, regular physical activity, and a minimally processed, traditional diet resembling a Paleolithic diet. Notably, in Kitavans, CRP was not associated with adiposity and showed weak inverse associations with total, LDL, and non-HDL cholesterol. Among Swedish controls, by contrast, CRP exhibited the expected positive association with adiposity and other cardiometabolic risk factors, consistent with findings from industrialized populations [54,74–76,249–253].

Paper II showed that Kitavans also had significantly lower total adiponectin concentrations than Swedish controls, a finding that was unexpected given their leanness, low CRP, and apparent absence of cardiometabolic disease. In the literature, total adiponectin often shows inverse associations with measures of overall and abdominal adiposity [94–100], with CRP [104–107], and with cardiometabolic risk [97,108–112,254,255]. The results therefore align with the adiponectin paradox, which holds that elevated total adiponectin does not invariably translate into better cardiometabolic outcomes [118]. The inverse association between Kitavan group and total adiponectin persisted after adjustment for multiple covariates (e.g., sex, age,

BMI, smoking status, and cardiometabolic comorbidities), supporting the existence of population-specific physiological baselines.

Together, Papers I and II indicate that low CRP and low total adiponectin may both reflect a healthy physiological state in lean, non-industrialized populations with minimal exposure to excess energy intake, ultra-processed foods, and sedentary lifestyles.

Paper III

Paper III tested the hypothesis that two healthy diets differing only in cereal-grain recommendations, one excluding all cereal grains and the other emphasizing whole grains in place of refined grains, when combined with or without exercise, would differentially affect abdominal adiposity as measured by waist circumference over 2 years. Although underpowered, the trial showed the largest between-group difference at 12 months, with the no-grain, no-exercise group reducing waist circumference by 4.4 cm more than the whole-grain, no-exercise group, corresponding to a moderate-to-large effect size. Albeit not significant, the result was borderline (p = .051). The lack of significance likely reflected the limited sample size, high variability within groups, and declining adherence rather than a true absence of effect. Importantly, the study illustrates the feasibility of implementing long-term dietary interventions in routine primary care.

Paper IV

Paper IV assessed the association between PDF, representing the proportion of total daily intake derived from food groups considered Paleolithic, and SLGCI biomarkers in a large population-based cohort. Significant inverse associations were observed between PDF and total leukocyte count, NLR, and CRP, even after adjustment for age, sex, physical activity level, BMI, smoking status, education level, living alone, born in Sweden, season of dietary data collection, and dietary method version. To our knowledge, this was the first study to simultaneously examine associations between PDF and all three SLGCI biomarkers. Including total leukocyte count and NLR expanded the inflammatory profiling typically used in nutritional epidemiology. In sensitivity analyses, the inverse associations between PDF and SLGCI biomarkers were broadly consistent across sex, age, and PDF strata. These results suggest that the anti-inflammatory potential of a Paleolithic dietary pattern may be at least partially independent of adiposity and consistent across multiple systemic inflammatory biomarkers.

Interpretation of findings

Together, the findings from Papers I through IV provide a multidimensional picture of how Paleolithic-style dietary patterns may influence SLGCI, both through reductions in abdominal adiposity and through the inclusion or exclusion of foods that directly affect the immune system.

Papers I and II highlight the value of cross-cultural comparisons. In Kitavans, CRP concentrations were lower than in Swedish controls despite high smoking prevalence and infectious exposures, and CRP did not vary with adiposity. These findings suggest that SLGCI may remain low under adverse exposures when protective lifestyle factors such as leanness, physical activity, and a traditional diet with similarities to a Paleolithic diet are present. By contrast, total adiponectin was lower in Kitavans, an unexpected result given their low overall and abdominal adiposity, reduced CRP, and apparent absence of cardiometabolic disease. This paradoxical finding raises questions about the interpretation of adiponectin as a biomarker of cardiometabolic health, since thresholds and meanings derived from industrialized populations may not apply to lean, traditionally living groups such as the Kitavans.

Paper III complements the findings from Papers I and II by experimentally testing one of the core features of the Paleolithic diet: the exclusion of cereal grains [155]. Although the study ended up lacking statistical power and found no significant between-group differences, the direction and magnitude of the observed effects suggest that this dietary feature may influence abdominal adiposity and warrants further investigation in adequately powered trials with stronger adherence support.

Paper IV provides epidemiological evidence that a higher PDF, reflecting a greater proportion of food intake consistent with a Paleolithic diet, is associated with lower SLGCI across total leukocyte count, NLR, and CRP.

Sensitivity analyses revealed an interaction between PDF and age for NLR, with explanatory power being greatest among older participants. This pattern aligns with the concept of inflammaging, whereby SLGCI becomes more prevalent with advancing age [256]. For CRP, the inverse association was significant only in the PDF tertile with the lowest PDF values, suggesting possible diminishing returns whereby individuals with the least Paleolithic-like food intakes may derive the greatest benefit from shifting toward a Paleolithic diet.

Exploratory analyses of food groups provided further context. Paleolithic food groups such as vegetables, fruits, and fish were inversely associated with inflammatory biomarkers, as expected [130–133]. Conversely, non-Paleolithic groups such as milk products and meat products (primarily processed meats) were positively associated. For milk and dairy, this finding does not align with systematic reviews and meta-analyses of RCTs, which generally report neutral or beneficial

effects on inflammation [209–211]. Nonetheless, the heterogeneity of dairy foods may result in divergent effects. In contrast, the association for meat products is consistent with evidence linking processed meat consumption to higher inflammatory biomarkers [257]. Importantly, associations for individual food groups were weaker than those for PDF, highlighting the value of using a dietary pattern measure such as PDF rather than focusing on single foods when evaluating diet-inflammation relationships.

Collectively, the findings of Paper IV are consistent with the hypothesis that SLGCI could act as a mediator on an indirect causal pathway between a Paleolithic diet and cardiometabolic disease. In this study, the mean PDF was about 40%, similar to the non-Paleolithic-diet arms of previous RCTs [161,162]. In contrast, the mean PDF in the Paleolithic-diet arms of those RCTs was closer to 80% [161,162]. Consuming a diet with a PDF of 80% instead of 40% would, based on the present associations, correspond to differences of about -0.33×10^9/L in total leukocyte count, −0.13 in NLR, and −0.21 mg/L in CRP. Prior work in the MDCS with a population of 25,969 individuals that linked these biomarkers to cardiometabolic disease incidence [29] suggests that such shifts could translate into an approximate 0.6–3.6% lower adjusted risk, equivalent to roughly 200 fewer cases out of 8,367 observed over 17.7 years.

Integrative perspective

The integrative nature of this thesis, spanning population comparisons, an experimental trial, and large-scale observational data, offers a comprehensive and triangulated assessment of the relationship between Paleolithic diet, abdominal adiposity, and SLGCI.

Taken together, the results from Papers I, III, and IV suggest that the exclusion of pro-inflammatory components (e.g., refined grains, added sugars, ultra-processed foods) [124–126], together with the inclusion of anti-inflammatory foods (e.g., fruits, vegetables, omega-3 rich seafood) [130–133,135], may decrease SLGCI through both a reduction in abdominal adiposity and through direct effects of diet on the immune system. These findings are particularly relevant in the context of previous literature, where systematic reviews and meta-analyses have reported inconsistent results for the Paleolithic diet and CRP [50,159,160]. Several factors likely contribute to this heterogeneity. First, relatively few trials of the Paleolithic diet have measured inflammatory biomarkers [159,160], and when they did, inflammation was often not the primary outcome [185,197,229,258–260], limiting statistical power to detect changes. Second, although most Paleolithic diet interventions exclude similar food categories (e.g., cereal grains, dairy, ultra-processed foods, added sugars, and the majority of added fats), the inclusion and relative emphasis on foods with anti-inflammatory

properties such as fish, fruits, and vegetables [130–133] can vary considerably between studies.

Importantly, the consistency of results in this thesis across culturally distinct populations and divergent methodological approaches increases confidence in their generalizability. The observed associations between PDF and SLGCI in a large-scale observational study also support the practical utility of PDF for future epidemiological and interventional investigations of diet-inflammation relationships.

Strengths

Papers I and II

A major strength of Papers I and II is the unique comparative design involving two markedly different populations: the Kitavans of Papua New Guinea and Swedish controls. This enabled cross-cultural analysis of circulating levels of CRP and total adiponectin under different ecological and lifestyle conditions. By comparing a lean, traditional-living population with an apparent absence of cardiometabolic disease to a European population with higher cardiometabolic risk, these studies provide valuable insights into how environment, diet, adiposity, and lifestyle relate to inflammatory and metabolic phenotypes.

Moreover, both studies benefited from standardized laboratory methods for biomarker quantification across the two groups, which strengthens internal validity for between-population comparisons. The use of well-characterized cohorts and rigorous anthropometric and biochemical assessments further support the interpretation of the observed associations between adiposity, inflammation, and cardiometabolic health. In addition, the alignment of the findings with principles from evolutionary medicine and anthropology adds theoretical depth.

These results extend current knowledge by providing comparative data from underrepresented, non-industrialized populations, thereby refining our understanding of physiological variation in systemic inflammation.

Paper III

This study's main strength lies in its real-world implementation as a long-term RCT in primary health care. Conducting the intervention in this setting enhances ecological validity and potential translation to clinical practice. By enrolling individuals with increased waist circumference and at least one additional

cardiovascular risk factor, the study targeted a population segment of high importance for cardiometabolic prevention.

Another strength was the factorial design, which allowed simultaneous testing of two dietary interventions, (exclusion of cereal grains vs. emphasis on whole grains) with and without exercise, enabling evaluation of independent and combined effects on waist circumference. The 2-year follow-up captured both short- and longer-term effects and provided insights into adherence dynamics over time.

Importantly, objective tools such as accelerometry, skinfold measurements, and bioelectrical impedance were used to assess physical activity and body composition, increasing methodological rigor. The dietary interventions were carefully structured to contrast two healthy diets differing only in cereal-grain content. Although the trial ended up being underpowered, the observed between-group difference in waist circumference at 12 months exceeded the magnitude anticipated in the pre-study power calculation, suggesting potentially meaningful effects that merit confirmation.

Paper IV

A major strength is the large sample size drawn from a well-characterized, population-based cohort, which enhances statistical power and external validity. The use of a validated, multimodal dietary assessment approach enabled estimation of individual dietary intake by weight, which in turn permitted calculation of PDF.

Furthermore, the inclusion of three complementary inflammatory biomarkers (total leukocyte count, NLR, and CRP) provided a more comprehensive assessment of SLGCI than studies relying on a single biomarker. The consistency of inverse associations across all three biomarkers strengthens confidence in the findings. Moreover, the fact that CRP was measured approximately 4 months after total leukocyte count and NLR, yet still showed significant correlations with them, reinforces their interpretation as biomarkers of chronic rather than transient inflammation.

Multivariate regression models adjusted for multiple potential confounders, including sociodemographic, lifestyle, and anthropometric variables, thus increasing internal validity. Notably, to our knowledge, this was the first study to examine PDF in relation to all three SLGCI biomarkers concurrently and to report inverse associations with both total leukocyte count and NLR, thereby making a novel contribution to the literature. Exploratory analyses of individual food groups showed associations in the same direction as the overall PDF findings, though smaller in magnitude, underscoring the added value of dietary pattern analysis over single-food assessments.

Limitations

Papers I and II

A primary limitation of Paper I is the reliance on a single CRP measurement to characterize inflammatory status. As noted in recent literature [248], single time-point assessments of CRP can be difficult to interpret in contexts like Kitava where acute infections are common [261,262]. CRP values can fluctuate substantially with transient immune activation, and within-individual variability may be particularly high in non-industrialized settings [263,264]. Thus, elevated CRP levels in some Kitavan participants may reflect short-term responses to infection or injury rather than persistent inflammatory states, whereas low values may simply miss episodic elevations not captured at the time of sampling.

Additionally, in Paper I, the inflammatory profile was assessed using only CRP, without additional biomarkers or functional immune measures, which could have provided more nuanced insights into immune status [265–269]. Although groups were matched on sex and age, residual confounding from unmeasured early-life exposures, infection history, or genetic background cannot be excluded. And while the Kitavan population represents a valuable model of low-cardiometabolic-risk, generalizability remains limited, particularly for populations undergoing rapid transitions in diet and lifestyle.

Moreover, several factors that can influence chronic inflammation were not assessed in Paper I and may contribute to observed differences between Kitavans and Swedish controls. These include environmental exposures such as air pollution [270], noise [271], and other urban stressors [272–274], as well as lifestyle-related variables such as sleep quality [275,276], circadian rhythm disruption [277,278], and psychosocial stress [279]. These factors are increasingly recognized as contributors to SLGCI, particularly in industrialized settings [3]. The gut microbiota is another unmeasured factor capable of influencing SLGCI [280,281]. Unfortunately, due to the historical nature of the Kitava data, collected in the early 1990s [214], when scientific interest, knowledge, and analytical technologies related to the human microbiome were still in their infancy, no microbiota data were collected. These unmeasured factors represent an important limitation when interpreting cross-population comparisons of inflammatory biomarkers and should be addressed in future studies.

Additionally, both Paper I and Paper II are limited by relatively small sample sizes and cross-sectional designs, which limit the ability to draw causal inferences and preclude the assessment of longitudinal changes in inflammation and cardiometabolic health. In Paper II, although total adiponectin was analyzed in relation to several covariates, factors known to affect adiponectin, such as specific dietary components [282], genetic variants [283], and circadian fluctuations [284–286], were not assessed or fully controlled for.

Finally, only total adiponectin was measured, without distinguishing between its biologically distinct isoforms. As noted above, adiponectin circulates in low-, medium-, and high-molecular-weight forms that differ in their biological activity [102,119]. While high-molecular-weight adiponectin is more strongly associated with improved insulin sensitivity and glucose homeostasis [120–122], the low-molecular-weight isoform has been proposed to exert more potent anti-inflammatory effects [102]. The reliance on total adiponectin precludes identification of isoform-specific associations and may partly explain inconsistencies in the literature, particularly in light of the adiponectin paradox [118], whereby elevated adiponectin levels have been associated with increased mortality in some populations [114,117]. Without isoform-specific data, it remains unclear whether the lower total adiponectin observed in Kitavans reflects decreased levels of a certain form, a shift in isoform distribution, or reduced total adiponectin with preserved anti-inflammatory capacity via lower-molecular-weight forms. Future studies should incorporate differential quantification of adiponectin isoforms to clarify their specific contributions to SLGCI and cardiometabolic risk in diverse populations.

Paper III

The most critical limitation of this trial was the resulting insufficient sample size. Despite extended recruitment efforts, only 73 participants were enrolled, well below the 200 estimated to detect a 2-cm between-group difference in waist circumference with adequate power. As a result, the study ended up being underpowered, reducing the probability of detecting statistically significant differences even when effects might be clinically relevant. Variability in waist-circumference change was also greater than anticipated, increasing the risk of type II error. This variability may have been exacerbated by the factorial design, which introduced complexity by combining two separate interventions and thereby increasing the potential for interaction effects or behavioral compensation that diluted the specific impact of either diet or exercise.

Adherence was another limitation. Short-term reductions in cereal-grain intake in the no-grain groups weakened over time, and differences between the diets were no longer evident by 24 months. Similarly, the exercise intervention showed mixed results, with initial increases in moderate-to-vigorous physical activity not sustained during follow-up. The absence of adherence monitoring at 3 and 6 months further limited the ability to assess early behavioral changes and their potential influence on waist circumference.

The reliance on self-reported 4-day weighed food records, although previously validated, represents another potential limitation, given the known vulnerability of such methods to reporting bias, particularly underreporting [287,288].

Finally, the study was conducted within the Swedish primary health care system, which may limit the generalizability of the findings to other health care settings with different structures and resources.

Paper IV

Despite its strengths, the study is not without limitations. First, dietary intake was assessed only once, precluding the ability to capture longitudinal changes in diet. Second, although the MDCS is prospective, the present analysis was cross-sectional, examining associations between baseline dietary data and inflammatory biomarkers. As noted previously, this design limits causal inference and the ability to establish temporal relationships. Furthermore, CRP was measured approximately 4 months after the baseline assessment of diet, lifestyle, and the other two biomarkers. This time lag may have introduced some temporal mismatch that could attenuate associations due to intervening exposures or acute events affecting inflammation. However, as noted in Strengths, CRP nonetheless remained significantly correlated with the other two SLGCI biomarkers despite the time lag, which is consistent with chronic rather than transient inflammation.

Third, the absolute magnitude of associations between PDF and inflammatory biomarkers was modest. Nevertheless, as mentioned above, prior work in the MDCS indicates that even small shifts in SLGCI biomarkers could translate into meaningful reductions in cardiometabolic disease burden at the population level [29]. Yet, achieving the increase in PDF required to produce such shifts (e.g., from 40% to 80%) may be challenging in real-world settings, which must be considered when evaluating public health impact.

Fourth, residual confounding cannot be ruled out despite comprehensive covariate adjustment. For example, unmeasured factors such as health-seeking behaviors may have contributed, as individuals with higher PDF may also engage in other preventive practices that lower systemic inflammation. Fifth, the cohort was predominantly composed of middle-aged Swedish women in an urban setting, limiting generalizability to other populations with different age distributions, as well as ethnic, cultural, and dietary backgrounds.

Finally, although the MDCS dietary method was carefully developed and validated [156,227,228], it still relied on self-reported data, which are inherently subject to recall and reporting biases [289–291]. The multi-method approach (7-day food record, 168-item FFQ, and structured interview) likely mitigated these sources of error to some extent, but residual bias cannot be excluded.

Conclusions and future perspectives

Paper I

CRP concentrations were markedly lower in Kitavans than in age- and sex-matched Swedish controls, suggesting that minimal baseline systemic inflammation may represent a physiological norm in populations characterized by low adiposity, regular physical activity, and traditional diets and lifestyles, even in the presence of pro-inflammatory exposures such as infections and smoking. However, the reliance on a single CRP measurement without repeated assessments or inclusion of additional inflammatory biomarkers limits interpretability and calls for caution in drawing definitive conclusions.

Paper II

Kitavans were also found to have significantly lower total adiponectin levels than Swedish controls, despite their favorable body composition and cardiometabolic profile. These results challenge the widely held view that higher adiponectin concentrations are indicative of more favorable cardiometabolic status and contribute to the ongoing debate surrounding the adiponectin paradox. Because only total adiponectin was measured, it is unclear whether the observed differences between Kitavans and Swedish controls reflect a reduction in a specific isoform, a shift in isoform distribution, or a preserved anti-inflammatory capacity despite lower total levels. This uncertainty may help explain inconsistencies in the literature and highlights the importance of future research incorporating isoform-specific assessments and broader adipokine profiling.

Paper III

The findings suggest that excluding cereal grains may help reduce abdominal adiposity. Although the trial ended up being underpowered with an unexpectedly high outcome variability, the direction and magnitude of the 12-month difference

indicate that this dietary strategy warrants confirmation in adequately powered studies.

The factorial design was informative but may have introduced unnecessary complexity, particularly given the mixed results of the exercise intervention. Future research should consider simplified designs focused exclusively on dietary interventions. Based on the lessons learned from this trial, a shorter 1-year, multicenter study that specifically examines the effects of cereal grains on waist circumference in at-risk populations appears both feasible and warranted.

Paper IV

Higher PDF was inversely associated with CRP, total leukocyte count, and NLR. These findings are consistent with the hypothesis that SLGCI may act as a mediator on an indirect causal pathway between the Paleolithic diet and reduced cardiometabolic disease risk, especially when considered alongside prior MDCS results associating higher PDF with lower cardiometabolic morbidity and mortality [156]. Moreover, this was the first study to examine PDF in relation to all three SLGCI biomarkers concurrently, and the consistent inverse associations strengthen the case for using PDF in diet-inflammation research. However, the observational and cross-sectional design, together with single time-point assessments of diet and inflammatory biomarkers, limits causal inference and the understanding of how these relationships evolve over time. Furthermore, the magnitude of the associations was modest, but, as previously noted, even small reductions in SLGCI may carry public health relevance when considered at the population level. Nevertheless, translating these findings into practice will require careful consideration of the feasibility of achieving and maintaining substantial increases in PDF in real-world settings.

General conclusion

Overall, the findings from this thesis support an inverse association between the Paleolithic diet and SLGCI. This relationship appears to operate through both reduced abdominal adiposity and the inclusion or exclusion of foods that directly affect the immune system. The findings are supported by the convergence of results across cross-cultural comparisons, an RCT, and large cohort analyses. In addition, the observation of unexpectedly low adiponectin concentrations in Kitavans despite leanness and apparent absence of cardiometabolic disease underscores the complexity of interpreting this adipokine and highlights the importance of population context when evaluating biomarkers. Finally, PDF proved useful as a

dietary pattern measure and should be considered in future epidemiological and interventional research.

Future perspectives

To advance the field, future studies should focus on clarifying the causal role of SLGCI in mediating the association between Paleolithic diet and cardiometabolic outcomes. This will require:

- Longitudinal and interventional studies that track changes in SLGCI biomarkers in response to dietary interventions varying in Paleolithic diet adherence, ideally with inflammation as a primary outcome.
- Mechanistic studies exploring the immunometabolic pathways linking diet to inflammation, including effects on gut microbiota, metabolic endotoxemia, redox balance, and inflammatory gene regulation.
- Adequately-powered RCTs using standardized and multidimensional inflammatory biomarkers (e.g., total leukocyte count, NLR, CRP, cytokine profiles).
- Inclusion of diverse populations, encompassing a range of socioeconomic, ethnic, and cultural backgrounds to enhance generalizability.
- Integration of digital adherence tools and real-time biomarkers to improve compliance monitoring and characterize dynamic inflammatory responses.

Ultimately, a deeper understanding of how the Paleolithic diet is associated with SLGCI may inform the development of novel strategies for preventing and managing cardiometabolic diseases.

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Paleolithic Diet, Abdominal Adiposity, and Systemic Low-grade Chronic Inflammation

PEDRO CARRERA BASTOS was born in Lisbon, Portugal, in 1975. After a decade in public administration following a degree in business administration, he changed path to the health sciences, completing a bachelor's in nutrition and dietetics and a master's in human nutrition. Encouraged by the late Staffan Lindeberg, he began a PhD at Lund University, which culminated in this thesis.

This thesis investigates associations among systemic low-grade chronic inflammation, abdominal adiposity, and Paleolithic-type dietary patterns using both observational and interventional designs.

The cover image highlights the thesis themes: diet, abdominal adiposity, and systemic low-grade chronic inflammation. It contrasts pro-inflammatory dietary patterns and greater abdominal adiposity on the left with anti-inflammatory foods and lower adiposity on the right. Central panels depict circulating leukocytes being recruited into tissues as inflammation rises.
Illustration by Carla Vidal. Created with BioRender.com.

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