The impact of social inequality on cardiometabolic disease risk in young adults

PhD dissertation

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Health

Aarhus University

2022

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Acknowledgements

I have many people to thank. First of all, my deepest gratitude goes to the participants in the West Jutland Cohort Study. Without their willingness there would be no dissertation.

My three supervisors complement each other in the best possible manner.

Johan. You are a truly remarkable person. Many newly hired colleagues notice how you grunt in the back of the room. However, it only takes a minute to appreciate your warmth, your enjoyable humor, generosity and willingness to fight for justice in multiple settings. Your stories from your time as a medical student, living in a commune and your activism as a young doctor are a great inspiration. I never doubted your support, and I know that the thought of you always having my back made me more courageous. Thank you!

Trine. The joke of you being like a mother to me is highly exaggerated. You are much too young! However, your protectionism toward me, your curiosity and your engagement in my research as well as my personal life may be underrated. Your door was always open to me. You challenged my decisions and made me argue my case without questioning my competences. You are a skilled epidemiologist, a great educator, and you always do your very best to give competent advice. Thank you for all the coffees, all the discussions and all of your support.

Morten. Your enthusiasm is extraordinary- even for a cardiologist. Any troubles or harsh comments by reviewers are "minor" to you. Some of the studies in this dissertation are quite different from your usual work. However, you were always very thorough in your feedback. The devil is in the detail and no skewed line would ever escape your eye. Thank you for your support, curiosity and endless optimism.

Many thanks to all of my colleagues and leaders at the Department of Occupational Medicine for creating an atmosphere of joy, laughter, competent feedback and respect. Thanks to fellow PhD students and teachers at various PhD courses. I truly appreciate the helpful and competent statistical guidance by *Morten Frydenberg* and *Stefan Nygaard Hansen*, and careful help with the literature search by *Jane Kjemtrup Andersen*. Thanks to the study nurses, radiographers and secretaries at Cardiovascular Research Unit, Department of Cardiology and Department of Radiology in Herning. Thanks to *Jens Melgaard Bruun* and colleagues at the Steno Diabetes Center Aarhus for opening the doors to the "Jungle" when my trip to Australia was cancelled.

A very special and heartfelt thanks goes to *Cecilie Rud Budtz* and *Søren Mose*. You became more than colleagues to me. You became valued friends. Cecilie, I value your frank manner and your pragmatic approach to life. I really appreciated all of our walks and talks and hope they will continue. Søren, your always empathic, well-considered and thorough thoughts are much appreciated. I feel lucky to share the time as a PhD student with you. Thank you!

My gratitude to friends and family defies words. However, a particular thanks goes to my parents, *Ulla* and *Orla Laursen*, for always encouraging me to explore the world, for endless support and love. My husband, *Bo*. Due to the pandemic, you became my closest colleague. Your steady workability and your effort to always perform your best have been a great motivation to me. However, most of all you are a fun, caring and loving husband and dad. You are indeed my dearest friend and the love of my live. I owe you everything. Last but not least, my two children Marius and Viola. Thank you for your playfulness, curiosity, love and honesty. You certainly made sure I never forgot the world outside academia. My love for you is endless.

Financial support

This PhD project was supported by grants from:

- The Karen Elise Jensen Foundation
- Health Research Foundation of Central Denmark Region
- The Research Foundation Goedstrup Hospital

None of the funding organizations had any influence on study design, analysis or interpretation of data.

Contents

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Preface

Motivation

Individuals with low socioeconomic position, on average, experience more risk factors, higher morbidity and increased premature mortality than individuals with high socioeconomic position. This inequality can be tracked throughout the life course. As a young doctor, working at the Regional Hospital in Herning, I soon recognized the pattern. I remember one late night at the Department of Pediatrics when an experienced nurse shared her mutual concerns. The next morning, I discussed it with colleagues during the clinical conference, and a few months later, the head of the department introduced me to professor Johan Hviid Andersen. Johan and his colleagues had been involved in multiple research projects concerning social inequality in health and had a great passion to unravel the underlying causes of these inequalities. Johan had just received a grant and was looking for a doctor to conduct one of the projects. Meeting Johan for the first time, being introduced to the West Jutland Cohort Study and listening to his summary of the social inequalities in health, I never doubted that this was an important issue. I felt absolutely fortunate to be able to seize the opportunity to explore early social determinants of cardiometabolic diseases. I had very limited knowledge about research, and the imposter syndrome tagged along most of the way. However, during my time as a PhD student I have gained confidence, experiences and competences that I will carry with me in the future as a clinician, a researcher and in my personal life.

I know this project is only a small piece in a wide-ranging and complex puzzle of social inequality in health. Nevertheless, I hope this research will increase the awareness of the inequalities in cardiometabolic diseases and contribute with knowledge about potentials

for early intervention in order to decrease the impact on future and present generations of children.

Mia Klinkvort Kempel,

Silkeborg, 2022

Outline of the dissertation

The dissertation is based on four papers from the project "*The impact of social inequality on cardiometabolic disease risk in young adults*". The project was carried out during my time as a PhD student in 2019–2022 at the Department of Occupational Medicine - University Research Clinic, Danish Ramazzini Centre, Goedstrup Hospital. Furthermore, the clinical health examination, on which this PhD project is based, was initiated in 2018 during my maternity leave prior to enrolment as a PhD student.

Chapter 1 provides an overview of the social determinants of cardiometabolic disease risk and an introduction to risk factors for cardiometabolic diseases. Chapter 2 outlines the overall and specific aims of the dissertation. Chapter 3 provides details about the material and methods used in the four studies. Chapter 4, 5 and 6 summarize the results of the four studies and provide discussions of the methods and findings. Chapter 7 and 8 provide main conclusions and future perspectives. Finally, an English and Danish summary are provided prior to listing the references, appendices and the four papers.

The four papers of the dissertation

Paper 1 **Kempel MK**, Winding TN, Lynggaard V, Brantlov S, Andersen JH and Böttcher M.

Traditional and novel cardiometabolic risk markers across strata of body mass index in young adults.

Published: Obes Sci Pract. 2021;7(6):727-737

Paper 2 **Kempel MK**, Winding TN, Böttcher M and Andersen JH.

Evaluating the association between socioeconomic position and cardiometabolic risk markers in young adulthood by different life course models.

Published: BMC Public Health 2022 Vol. 22 Issue 1 Pages 694

Paper 3 **Kempel MK**, Winding TN, Böttcher M, Hansen SN and Andersen JH.

Childhood socioeconomic position and cardiometabolic risk in young adulthood- the impact of mental health.

Submitted to PLOS ONE

Paper 4 **Kempel MK**, Winding TN, Böttcher M and Andersen JH.

Subjective social status and cardiometabolic risk markers in young adults.

Published: Psychoneuroendocrinology 2022 Vol. 137 Pages 105666

Additional papers co-authored during my time as a PhD student

Paper 5 Dahl T, Bakmand L, Jakobsgaard MØ, **Kempel MK**, Böttcher M, Winther S and Schmidt SE.

Effect of obesity in young adults on an acoustic-based system for ruling-out coronary artery disease.

Submitted to The International Journal of Cardiovascular Imaging

Paper 6 Søndergaard SM, Winding TN, Lynggaard V and **Kempel MK**

Sustained physical activity and cardiometabolic risk markers in young adulthood- a prospective cohort study

Manuscript *in draft*

Abbreviations

ABC	Aboriginal Birth Cohort
ADD Health	National Longitudinal Study of Adolescent to Adult Health
AL	allostatic load
APCAPS	Andhra Pradesh Children and Parents' Study
BMI	body mass index
CAC	coronary artery calcification
CARDIA	Coronary Artery Risk Development in Young Adults
CI	confidence interval
CMR	cardiometabolic risk
CVD	cardiovascular disease
DAG	directed acyclic graph
DBP	diastolic blood pressure
DRM	diagonal reference models
ELSA	the English Longitudinal Study of Ageing
ELSA-Brasil	The Brazilian Longitudinal Study of Adult Health
HbA1c	glycosylated hemoglobin

HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HDL-C	High density lipoprotein cholesterol
HR	heart rate
HRS	Health and Retirement Study
Hs-CRP	high sensitive C-reactive protein
HOMA-IR	homeostatic assessment model of insulin resistance
ICAM-1	intercellular adhesion molecule-1
ICD	international statistical classification of diseases and related health problems
IL-6	Interleukin-6
JHS	The Jackson Heart Study
IMS	Indian Migration Study
KNHANES	the Korea National Health and Nutrition Examination Survey
HTN	hypertension
LDL-C	low density lipoprotein cholesterol
MeSH	medical subject heading
MHAS	Mexican Health and Aging Study
MIDUS	National Survey of the Midlife Development in the United States

MUSP	Mater-University of Queensland Study of Pregnancy
NHANES	National Health and Nutrition Examinations Survey
NSHD	National Survey of Health and Development
OECD	The Organisation for Economic Co-operation and Development
RODAM	Research on Obesity and Diabetes among African Migrants
SAGE	Study on Global Ageing and Adult Health
SBP	systolic blood pressure
SEP	Socioeconomic position
SLI	Standard of living index
SSS	subjective social status
SWAN	the Study of Women's Health Across the Nation
T2D	type 2 diabetes
TC	total cholesterol
TG	triglycerides
TNF	Tumor necrosis factor
VCAM-1	vascular cell adhesion molecule-1

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Chapter 1, Introduction

Cardiometabolic diseases are the leading causes of mortality and morbidity in adult populations worldwide(1). Cardiometabolic diseases cover a wide range of diseases including coronary artery disease, diabetes mellitus and stroke. These diseases primarily occur in middle- and older-aged individuals(2). However, cardiovascular damage and metabolic abnormalities, e.g. development of fibrous plaque lesions, unfavorable lipid profile, increased blood pressure and plasma glucose levels, may initiate in childhood and youth and continue into adulthood(3-7). Cardiometabolic diseases are multifactorial(8, 9). Traditional risk factors include genetic and epi-genetic pre-disposition, overweight/obesity, age and unhealthy lifestyle(10-13). Most recently, psychological distress was recognized as an independent risk factor for the development of cardiometabolic diseases(14-17). Various combinations of these risk factors might trigger pathophysiological processes leading to downstream pathologies such as formation of atherosclerotic plaques(8, 10, 18). In addition, individuals from a lower socioeconomic position (SEP) have an increased cardiometabolic disease risk compared to individuals from a higher SEP(19-21). This inequality is evident throughout the life course, and mounting evidence suggests it is rooted in childhood(22, 23). Cardiometabolic diseases are some of the most widely examined diseases within the field of health inequality. Nevertheless, complete knowledge about the intertwined causes and mechanisms generating this inequality is as yet unattained(24). Given the modifiability of many cardiometabolic risk factors, it seems crucial to investigate causes in the young age group to facilitate early intervention, with potential implications throughout life. This includes an improved understanding of the inverse association between childhood SEP and

cardiometabolic disease risk in order to identify targets for prevention to protect the future cardiometabolic health of children across all strata of SEP.

The following sections introduce the social determinants of health and summarize the current knowledge concerning socioeconomic inequality in cardiometabolic disease risk with a primary focus on childhood SEP. It is not my ambition to provide a complete review of the vast literature. However, the intention is to highlight important and novel findings and illustrate hypotheses regarding the underlying mechanisms of the association between childhood SEP and later cardiometabolic disease risk.

Social determinants of health

Research in relation to inequalities in health increased during the last part of the 20th century(25). This research was mainly driven by large epidemiological studies. A prominent example is the research by Michael Marmot among British civil servants in the Whitehall study(26). The study found inverse associations between grade of employment and mortality from coronary heart disease. Moreover, the association remained strong after taking other known risk factors such as smoking and leisure time physical activity into account. Additionally, Ben-Shlomo and Kuh proposed the intuitively obvious, however empirically complex, life course approach to social determinants of chronic diseases(27). This life course approach refers to "*the study of long-term effects of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life. It includes studies of the biological, behavioral and psychosocial pathways that operate across an individual's life course, as well as across generations*"(27, 28). Integrating a life course approach in epidemiological research highlights the specific

contribution of childhood SEP to adult cardiometabolic disease risk(23). I will elaborate more on the life course framework later in this chapter. The World Health Organization defines the social determinants of health as "..*the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life*"(29). This rather broad definition underlines the complexity within the field. Various indicators with various meanings and interpretations are used to measure SEP in relation to health at different ages(30). It is unlikely that any of the indicators of SEP directly affect health in a causal manor. However, the SEP indicators reflect other circumstances in life that might explain the associations with health. Below, I will introduce the main indicators of SEP, and present what aspects in life each indicator primarily reflects. Additionally, other important approaches to evaluate social circumstances include ethnicity, sexuality, various measures of adverse childhood experiences and composite measures of multiple SEP indicators that are not touched upon in this dissertation.

Indicators of socioeconomic position

Education

Education is a widely used indicator of SEP, and one of its strengths is that it remains stable for most people from early adulthood onwards(20). Most studies categorize the level of education into specific achievements such as low/high or primary, secondary and tertiary education, whereas others use it as a continuous score(30). Education reflects cognitive and psychological resources(30). Furthermore, education can be correlated with other indicators such as occupation and income and thereby reflect material

resources(31). Additionally, education may reflect the level of health literacy and thus influence the ability of an individual to comprehend health messages and communicate with health care professionals(32).

Income

Income is the indicator that most directly reflects material resources, i.e. the ability to buy food, housing and leisure time activities. Furthermore, income might also affect the ability to access health care facilities and education(20, 30). In contrast to educational level, the income indicator may fluctuate across the life course and is consequently vulnerable to the time of measurement. Most studies measure income as household income, and some take the family size and context into account and calculate equivalized household income(20). As with education, income can be measured as a categorical or continuous indicator and furthermore as a relative indicator by specifying levels of poverty in a given society(30).

Occupation

Occupation is correlated with income and correspondingly reflects material resources. Furthermore, occupation might also reflect social standing, social network, work exposures (toxics, psychosocial or physical) and access to better health care through work-related insurance(20, 32).

Neighborhood and household conditions

Neighborhood and household conditions reflect material resources. Moreover, they may reflect overcrowding and exposure to poor building materials or air pollution in addition to access to running water, green spaces, healthy food and bike lanes(30). Furthermore,

the characteristics of the neighborhood may reflect health behaviors among the residents and thereby indicate individual level health behaviors(33).

Subjective social status

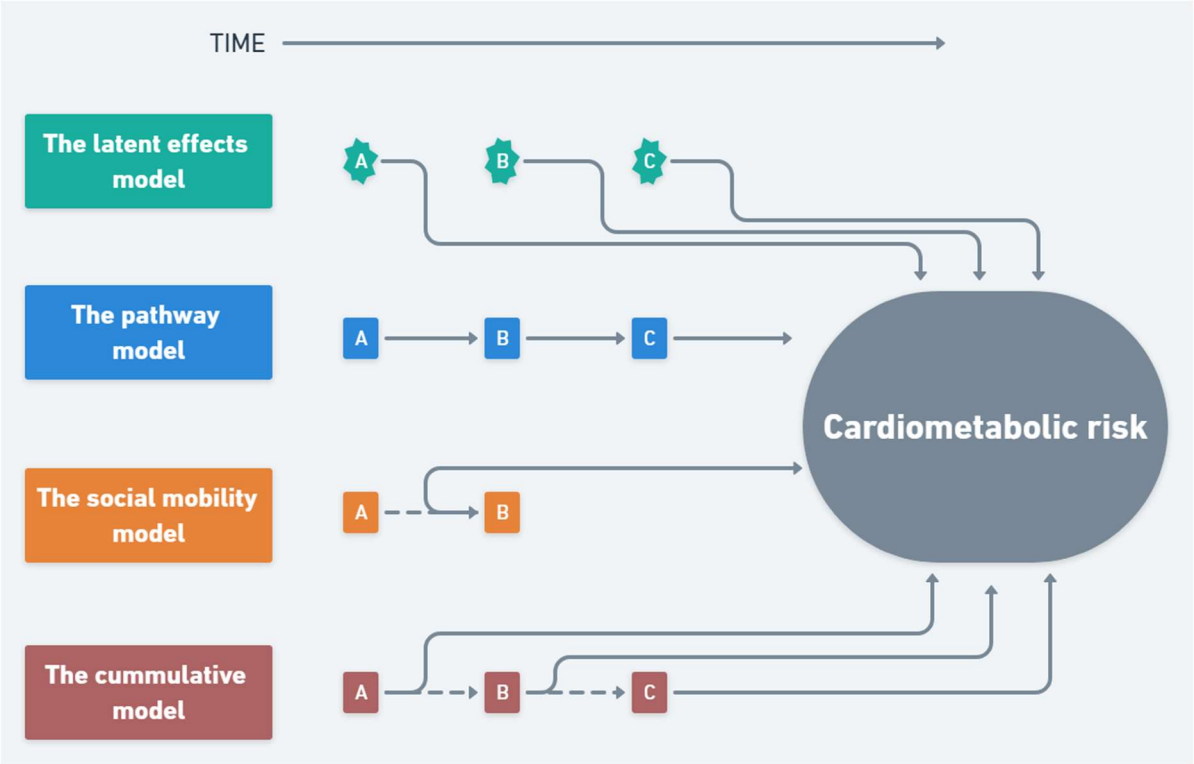
As opposed to the abovementioned objective indicators of SEP, subjective social status (SSS) is the perception of own (family) status in the social hierarchy. Most often SSS is measured by the MacArthur Scale, a pictorial 10-rung ladder scale, with higher scores indicating higher perceived social status(34, 35). As with income and education, the measure is used as a continuous or categorical measure. However, there is no consensus about cut-off thresholds. For example McClain et al. categorized at the median (step 5), Singh-Manoux et al. categorized into five categories of two steps each, and Ferreira et al. dichotomized into low (steps 1–4) and high (steps 5–10)(36-38). The predictive value of this indicator remains a topic of debate in the literature. Some researchers argue that SSS acts as an intermediate in the relationship between objective measures of SEP and health, whereas others state that SSS provides unique information including lifetime accumulation of experiences, achievements and social interactions that are not fully captured by objective measures of SEP(39, 40).

The life course framework

Examining cardiometabolic disease etiology within a life course framework increases the awareness of potential long-term effects from exposures early in life(22, 27). In addition to the different indicators of SEP, various life course models have been conceptualized concerning the influence of childhood SEP on later disease risk. The four most common life course models are the latent effects model, the pathway model, the social mobility

model and the cumulative model(22, 41, 42). The models are not mutually exclusive as some of the underlying hypotheses might overlap. However, methodological differences and the different interpretations of the life course illustrate different potentials for intervention and implications from exposure to a low SEP in childhood. A simplified illustration of the four life course models is presented in Figure 1.

Figure 1. Simplified illustration of the four life course frameworks



A, B and C represent exposures in a temporal ordering.

The latent effects model hypothesizes a direct effect on disease risk from early life exposure independent of later life experiences(27, 43, 44). Different periods in early life are proposed as critical/sensitive periods that permanently influence later disease risk. These periods include prenatal, early, middle and late childhood(45-47). The pathway model on the other hand hypothesizes a continuity of circumstances where early life exposure to low SEP influences later life experiences via pathway effects(27, 43, 48). Accordingly, later life experiences (behavioral, psychosocial and environmental) are

influenced by early life exposures acting as intermediates on the path from a low SEP to disease risk. The social mobility model hypothesizes a specific impact on disease risk from intergenerational social mobility, i.e. moving upwards or downwards on the social ladder compared to the previous generation. However, different theories propose different effects from upward/downward social mobility and consensus as to the direction of the impact on disease risk is yet uncertain within the social mobility literature(49-51). The fourth life course model is the cumulative model. This model hypothesizes that accumulated exposures across the life course impact disease risk(27, 28). The model thus focuses on the duration of exposure rather than the timing of exposure.

A systematic review by Pollitt et al. evaluated the evidence for the four life course models in relation to cardiovascular outcomes(22). The authors concluded that the cumulative model was most consistently supported in the literature compared to the other models. However, varying methodology and study designs made the direct comparison of the life course models across different studies difficult. Consequently, the authors recommend researchers to evaluate cardiovascular risk factors in early and middle adulthood by multiple life course models simultaneously within the same data. The authors furthermore recommend the use of different SEP indicators.

Measures of biology in studies of cardiometabolic disease risk inequality

It is not entirely clear how differences in social circumstances "get under the skin" and translate into inequality in cardiometabolic disease risk (52). However, the incorporation

of biological measures in the investigation of social stratification and health has gained much attention within the last 30 years, and multiple biomarkers have been proposed as risk markers in the relationship between a low SEP and manifest cardiometabolic diseases(53-55). A low SEP is suggested to cause dysregulation of multiple biological systems including the immune, neuroendocrine, metabolic and cardiovascular systems(55-57). Individual biomarkers that are frequently investigated in relation to cardiometabolic disease risk inequalities include blood pressure, measures of anthropometry, lipids, glucose and most recently inflammatory markers(22, 53, 58-62). Furthermore, researchers have struggled to develop more comprehensive composite measures to capture the overall disease risk of the individual. This work is motivated by clinical knowledge that risk markers tend to cluster and is consistent with growing evidence that various (patho)physiological systems interact, with changes in one system leading to changes in others, increasing disease risk(57, 63, 64). Furthermore, minor increases across multiple risk markers can lead to increases in overall disease risk despite none of the individual risk markers exceeding clinically established thresholds(63, 65, 66). The development of composite measures across different biological systems attempts to integrate the potential additive/synergistic effects that work across different pathophysiological systems prior to manifest diseases. One of the approaches is defined by the metabolic syndrome (also known as the insulin resistance syndrome, cardiovascular risk factor cluster or Syndrome X)(67, 68). The metabolic syndrome has had various definitions over time but all include abdominal obesity, dyslipidemia, glucose intolerance and hypertension(69). Each definition dichotomizes the incorporated biomarkers and the final outcome. This binary approach and the thought of a unique pathophysiological condition have been criticized. Consequently, recent research

proposes continuous measures of the metabolic syndrome to avoid arbitrary thresholds, particularly among younger individuals(67, 70, 71). In 2006, the International Diabetes Federation suggested a worldwide definition of the syndrome and furthermore encouraged researchers to include novel biomarkers, e.g. markers of inflammation, in future studies to help modify and validate the definition(68). Nevertheless, the metabolic syndrome has demonstrated that the presence of multiple risk markers is strongly correlated with later manifest cardiometabolic diseases(72, 73). Similarly, research evaluating physiological wear-and-tear by the allostatic load index has revealed associations with later risk of cardiometabolic diseases(74). Allostatic load index is a combined measure of autonomic, metabolic, endocrine and immune biomarkers evaluating the biological adaptation to external stressors(75). The index is based on the assumption that a normal allostatic response results in elevated levels of allostatic biomarkers for a short period of time in order to help the body maintain stability. If the stressor remains, the allostatic biomarkers remain elevated, resulting in increased cardiometabolic disease risk(76). The initial definition was based on data from the MacArthur studies of successful aging and was an individual sum-score of how many of the ten included biomarkers were in the upper risk quartile of the sample selection(77). Since then, the allostatic load index has been modified a number of times and considerable research suggests that the combined measure outperforms each of the individual biomarkers in prediction of later cardiometabolic diseases(66, 78-80). Additional work from multiple epidemiological studies, e.g. the 1958 British Birth Cohort, the National Health and Nutrition Examinations Survey (NHANES), Coronary Artery Risk Development in Young Adults (CARDIA) and the National Longitudinal Study of Adolescent to Adult Health (Add Health), use different composite measures to assess cardiometabolic

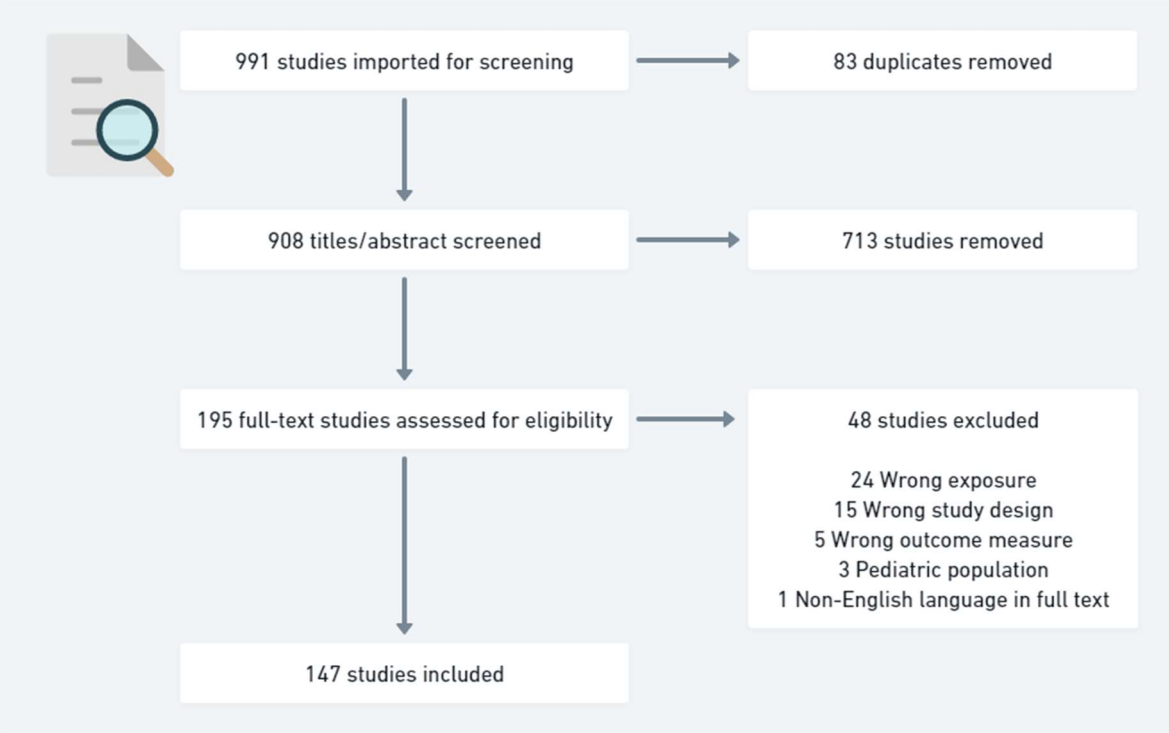
disease risk(81-88). Common to all of the measures is the inclusion of multiple biomarkers across different biological systems, most of which are constituents of the metabolic syndrome or the allostatic load index. However, the construction of the composite measure varies between the studies. Some are generated from cluster analyses defining high/low risk individuals, others are continuous measures based on sample-specific z-scores and others are sum-scores based on clinical thresholds for each biomarker or sample-specific distributions (e.g. quartile-based).

Childhood socioeconomic position and cardiometabolic disease risk

We used PubMed, PsycInfo and Embase to review the literature concerning the association between childhood SEP, intergenerational social mobility and cardiometabolic disease risk in adulthood. The search was performed in January 2022. The search query and outcome of the search are presented in Appendix 1. Initially, titles and abstracts were screened and relevant papers were selected for full text review. Original papers were included if relevant outcome measures[1] were obtained in adulthood (≥ age 18), childhood SEP was included as exposure measure and the study design was observational. A flowchart depicting the procedure is shown in Figure 2.

[1] Outcome measures included manifest cardiometabolic disease, distinct cardiometabolic risk markers and various composite measures including the metabolic syndrome and allostatic load index. We did not include studies that exclusively evaluated measures of anthropometry.

Figure 2. Visual summary of the screening process of literature investigating childhood SEP and adult cardiometabolic disease risk

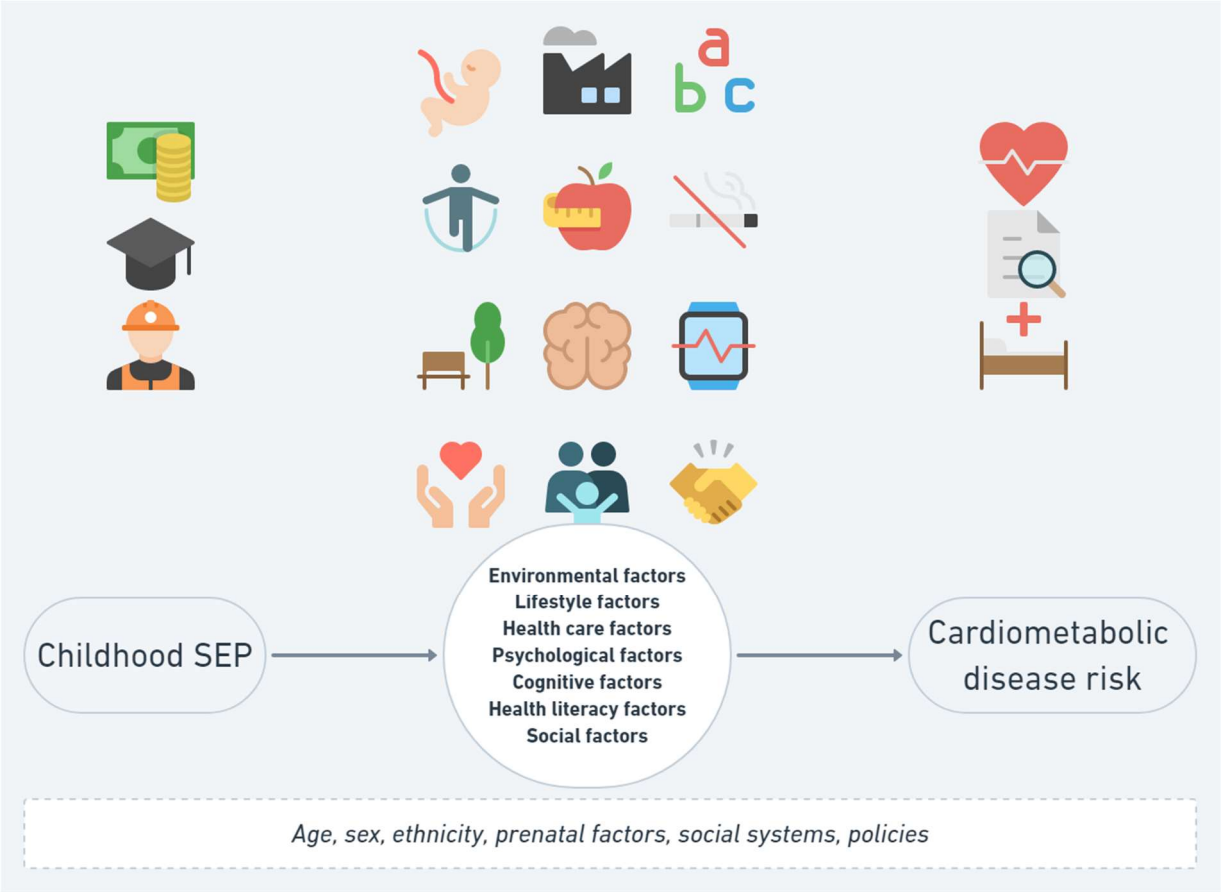


A schematic summary of the literature restricted to the time period January 2016 to January 2022 (N = 49) is presented in Appendix 2. Furthermore, papers prior to this period are also referenced throughout the dissertation. To include novel papers that are not yet indexed with MeSH terms, we supplemented with a search restricted to the last year using text words rather than MeSH terms in April 2022. We also did a review of the literature evaluating the association between SSS and cardiometabolic disease risk in adulthood. The search query and a schematic summary of relevant original studies without time-restriction (N = 23) are presented in Appendix 3, excluding study 4 of this dissertation.

Uncovering the "why" - potential mechanisms linking childhood socioeconomic position and cardiometabolic disease risk

Our assessment exposes the manifold indicators of SEP and measures of cardiometabolic disease risk used in the literature. Notwithstanding, there is a clear tendency toward an association between various indicators of low childhood SEP and increased cardiometabolic disease risk in adulthood. On the other hand, the studies explicitly evaluating life course models, especially the impact of intergenerational social mobility, display some inconsistency(22, 89-93). Furthermore, worth noticing, the social gradient is reversed in studies examining populations from middle income countries and among children born to indigenous Australian mothers(94-97). The study of "why" has gained increased attention within the past decades; however, the majority of studies designate the association between a low childhood SEP and increased cardiometabolic disease risk without exploring the underlying mechanisms. As can be seen in the schematic summary, many studies include adult SEP and find a buffering impact of a high adult SEP. However, as this in itself is an indicator of other aspects in life, it does not fully offer an explanation of the association. Differences across SEP in prenatal, postnatal and childhood environments (physical and emotional), lifestyle factors, health literacy, health care and psychological factors are suggested as potential causal factors in the association between childhood SEP and later cardiometabolic disease risk(61, 98-105). Figure 3 illustrates some of the factors that might be involved in the association.

Figure 3. Conceptual model of the association between childhood SEP and cardiometabolic disease risk

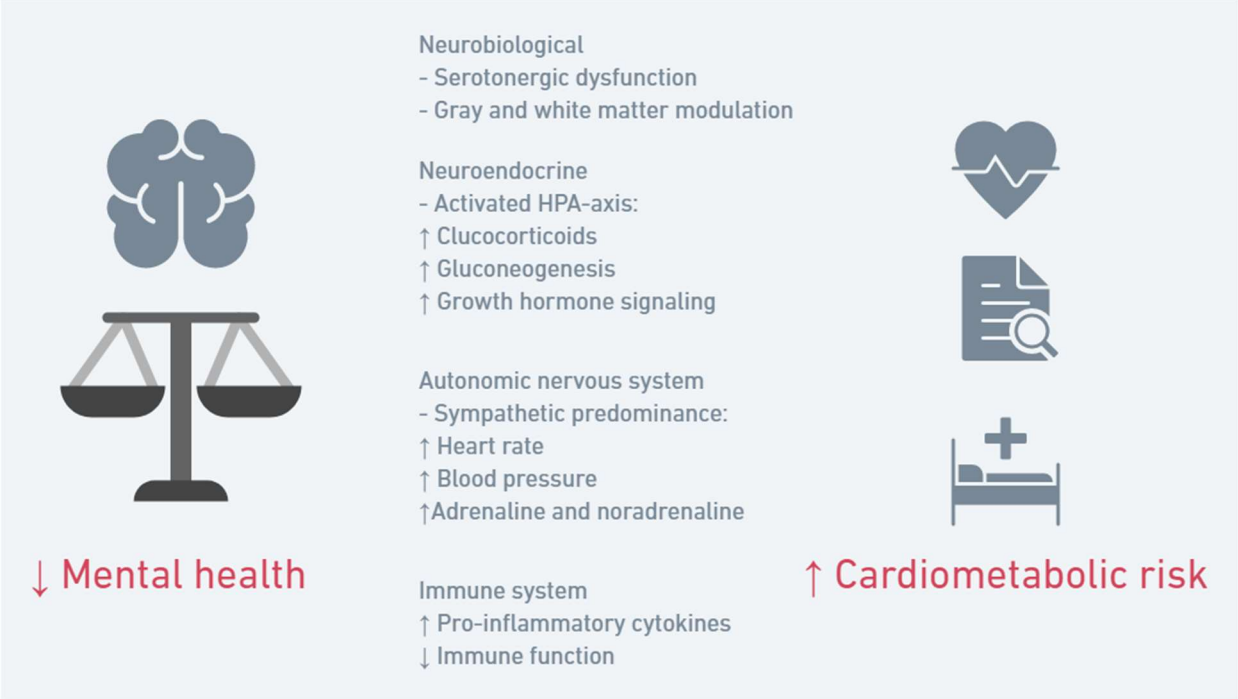


A study from the 1958 British birth Cohort (N = 7,573) found inverse associations between two measures of childhood SEP and allostatic load at age 44(103). After including financial, psychosocial, educational and lifestyle factors at ages 7 to 23 years, 45–60% of the associations remained unexplained. Furthermore, the relative importance of each intermediate is yet undetermined.

The next section focuses on the hypothesized relationship between childhood SEP, psychological factors and cardiometabolic disease risk. Children growing up in families with a low SEP, on average, experience more mental health problems than children growing up in families with a high SEP(106, 107). These include higher levels of perceived stress, depressive symptoms and a lower degree of self-esteem and coherence, which have been linked to increased cardiometabolic disease risk(14, 17, 61). Current evidence

suggests that psychological factors work in multiple ways with regard to cardiometabolic disease risk. Direct pathophysiological effects include neurobiological changes, altered neuroendocrine and autonomic function and low-grade inflammation(14, 59, 98, 108-111). Figure 4 summarizes some of the biological systems and early cardiometabolic effects involved in the association between psychological distress and cardiometabolic disease risk.

Figure 4. Cardiometabolic (patho)physiological effects of psychological distress



These direct pathophysiological effects are interrelated (i.e. pro-inflammatory cytokines stimulate the hypothalamus-pituitary-adrenal (HPA)-axis) and may be augmented by further indirect effects operating through lifestyle factors (i.e. physical inactivity and smoking), attained educational level/adult SEP and health literacy(112-114). Altogether, this puts forward the hypothesis of a mediating effect of mental health on the association between childhood SEP and cardiometabolic disease risk.

Synthesis

Cardiometabolic diseases are the main causes of premature mortality and morbidity in adult populations worldwide. Because of aging populations and an increasing number of children and young adults with obesity, knowledge about the biology of cardiometabolic diseases is crucial. This includes improved understanding of the underlying pathologies of obesity and adverse social circumstances. Individuals growing up in families with a low childhood SEP experience increased cardiometabolic disease risk compared to individuals growing up in families with a high SEP. However, exact knowledge about how the social circumstances "get under the skin" has not yet been achieved. Various risk factors accumulate in low SEP environments. These include unhealthy lifestyle and environmental pollutants. Nevertheless, this does not explain the full association. Little is known about the potential impact of mental health on the association. Improved understanding of potential pathways is critical to inform policy makers and improve upstream cardiometabolic prevention strategies to support the continuing health of all children, including those growing up in families with a lower SEP.

2

Chapter 2, Aims

The overall aim of my PhD project is to empirically examine the association between childhood SEP and later cardiometabolic disease risk in young Danish adults. The ultimate purpose is to gain insight into modifiable risk factors in order to outline future perspectives that can decrease the social inequality in cardiometabolic diseases.

Study 1

Specific aim: To evaluate various cardiometabolic disease risk markers across strata of body mass index (BMI) and sex in young adulthood.

Study 2

Specific aim: To evaluate the association between childhood SEP (educational level of the mother and household income) and cardiometabolic disease risk in young adulthood using four life course models.

Study 3

Specific aim: To evaluate the mediating impact of psychological factors on the association between parental educational level and cardiometabolic disease risk in young adulthood.

Study 4

Specific aim: To evaluate the association between subjective social status at ages 15 and 28 and cardiometabolic disease risk in young adulthood.

3

Chapter 3, Data sources and methods

The West Jutland Cohort Study

The West Jutland Cohort Study initiated in 2004. The main purpose of the cohort study was to investigate various aspects of social inequalities in health and well-being in a life course perspective. The cohort was a complete regional sample of all individuals born in 1989 and living in the former county of Ringkoebing in Western Jutland, Denmark, when the study initiated. The source population comprised 3,681 individuals who were identified by information from public schools and the Central Office of Civil Registration using the Danish personal identification number (CPR number). The studies summarized in this dissertation include information from questionnaire rounds in 2004, 2007, 2010 and 2017. The entire source population (N = 3,681) was re-invited to respond to questionnaires in all rounds except those who emigrated, died or contacted the research group asking to be excluded from future questionnaires. The questionnaires included information about psychological, physical and social health. All questionnaires were in Danish and are available in full length at www.vestliv.dk. The first questionnaire round was in 2004. Participants were at that time approximately 15 years old. They were asked to complete the questionnaires during school hours. Those who did not attend school on the specific day received the questionnaire by postal mail. The second questionnaire round was in 2007, when the participants were approximately 18 years old, using electronic and postal questionnaires. The third and fourth questionnaire rounds were in 2010 and 2017, when the participants were approximately 21 and 28 years old, using electronic questionnaires. Furthermore, the biological parents of the participants

received a questionnaire in 2004 concerning psychological, physical and social health of themselves and the participants.

The clinical health examination

To gain knowledge about subclinical cardiometabolic disease risk in young adulthood, we invited a subsample (n = 264, 50% women) of the West Jutland Cohort to a clinical health examination at ages 28–30. We did a sample size calculation (power-calculation) before we initiated the recruitment. The sample size calculation was based on the expected carotid intima-media thickness determined by ultrasound measurements across three BMI groups of normal weight, overweight and obese individuals[2]. Afterwards, the exact number of 264 was chosen based on suitability because some of the biochemical analyses were performed on plates of each 88 individuals (88 x 3 = 264). The questionnaire in 2017 included the opportunity to take part in the health examination. The questionnaire respondent indicated: "not interested", "want to learn more" or "interested". Criteria for the inclusion and exclusion of individuals with regard to the clinical health examination are presented in Table 1. Furthermore, a flow-chart of response-rates for each questionnaire round and the sampling procedure of the study population are provided in Figure 5.

[2] Due to measurement error of the carotid intima-media thickness, these measurements were not included in any of the final studies and will not be presented in the dissertation.

Table 1. Inclusion and exclusion criteria for invitation to clinical health examination

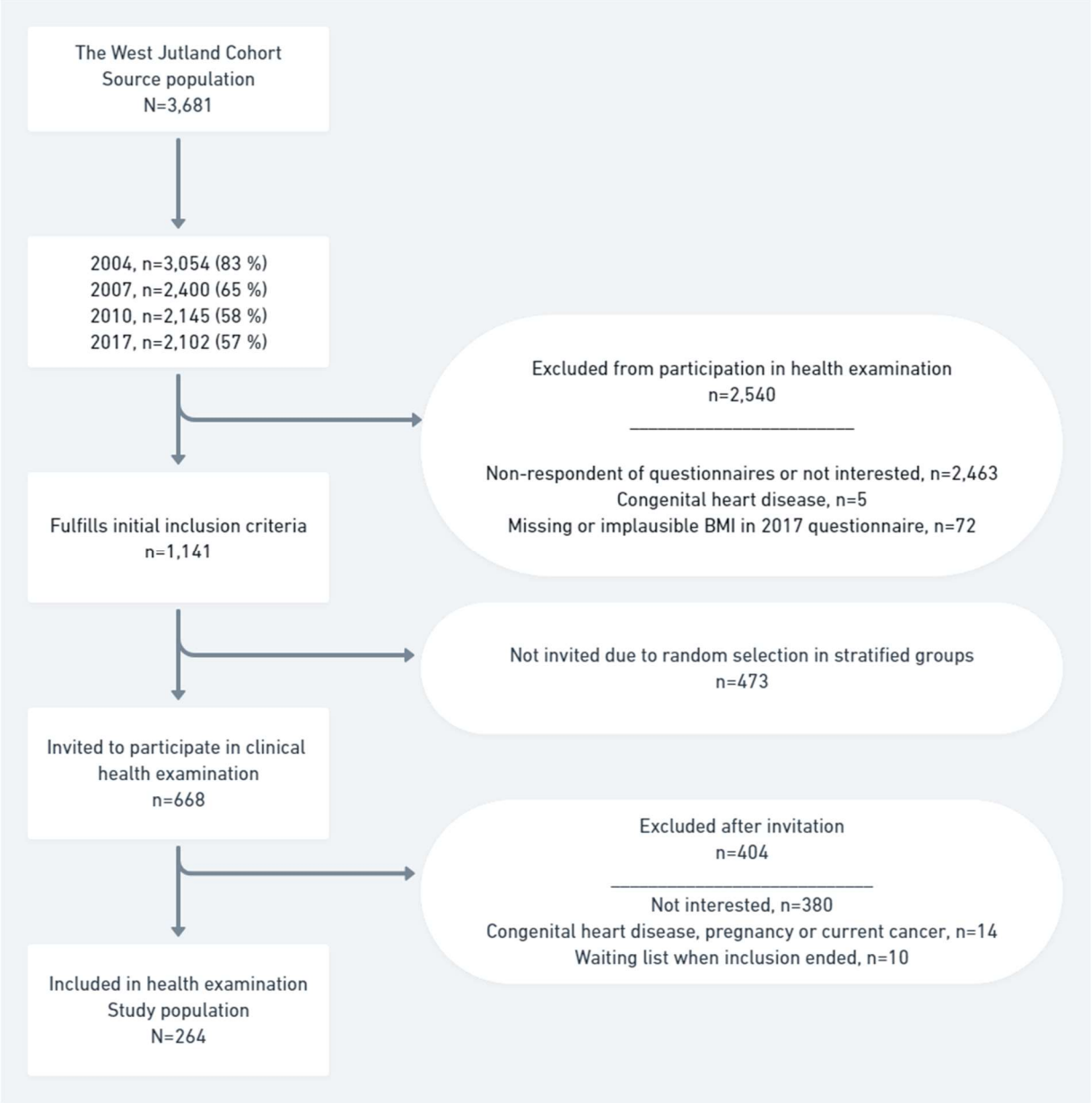
Inclusion criteria	Respondent of questionnaire in 2004 Respondent of questionnaire in 2017 Indication of interest in clinical health examination ("want to learn more" or "interested")
Exclusion criteria	Congenital heart disease Missing or implausible height and/or weight in questionnaire in 2017 Severe claustrophobia or weight >300 kg Active cancer disease Pregnancy (if feasible during the inclusion period pregnant participants were included after giving birth)

To ensure variety of individuals in the study population, those fulfilling the initial criteria (n = 1,141) were stratified based on sex and latest self-reported height and weight (BMI >25, 25–30 and >30 kg/m^2) into six groups. Within each group, potential participants were randomly sampled (n = 668) and provided detailed information about the clinical health examination through their nationally required electronic mailbox. A reminder was sent out to those not responding to the first invitation. The initial hope was to include 44 participants in each BMI group of each sex. Due to lack of participants with a self-reported BMI >30 kg/m^2, this was not obtained and more from the group with self-reported BMI 25-30 kg/m^2 were invited. Invitations were sent out in five differentiated rounds depending on the number needed in each sex and BMI group.

The clinical health examinations were initiated in April 2018 and completed in December 2019. All biochemical analyses were performed in March 2020. The health examination included computed tomography of the heart, bio-impedance analysis, measures of body

composition, blood pressure measurements and a panel of circulating cardiometabolic risk markers. The procedures and measurements are described in detail in paper 1(115). Furthermore, the participants in the health examination received a questionnaire regarding parental cardiometabolic disease history and own smoking habits prior to the health examination.

Figure 5. Flowchart of the study population



Register information

Statistics Denmark

Statistics Denmark is the central authority on Danish statistics and provides access to pseudonymized data from various Danish registers. Individual-level linkage of all register, questionnaire and clinical data was possible using the CPR number as identifier. Afterwards pseudonymized data were accessible at the Research Server of Statistics Denmark, where all analyses reported in this dissertation were conducted. Registers of relevance were provided by Statistics Denmark and are described below.

The Danish Civil Registration System

The Danish Civil Registration System holds updated information about date of birth, sex, civil status, vital status and migration status from 1968 onwards(116). In the studies summarized in this dissertation, the register was used to identify the study population, the biological sex and to link information about the parents and the participants.

The Danish Education Registers

The Danish Education Registers link individual-level information from surveys and the administrative records of the education institutions on students enrolled in Denmark. We used information from the Population's Education Register, which contains information about the highest completed educational level. The registers only provide information about educations authorized by the Danish Ministry of Education and do not automatically include education completed outside of Denmark(117). In the studies summarized in this dissertation, we used information on the educational level of the father, the mother and the study participants.

The Income Statistics Register

The Income Statistics Register provides detailed information regarding wages, transfer payments, capital income and public pensions from 1970 onwards on everyone who is economically active in Denmark(118). In the studies summarized in this dissertation, information about childhood household income was used.

The Danish National Patient Register

The Danish National Patient Register is a nationwide register that contains electronically submitted information from public hospitals(119). Dating back to 1977, all inpatient somatic care was included, and from 1995 onwards all somatic and psychiatric inpatient and outpatient care was included. The coding system of the register is the International Classification of Diseases (ICD). In 1994, the ICD-10 replaced the former ICD-8 (ICD-9 was never implemented in Denmark). In the studies summarized in this dissertation, information about parental cardiometabolic diagnoses from 1995–2018 was used.

The Danish Medical Birth register

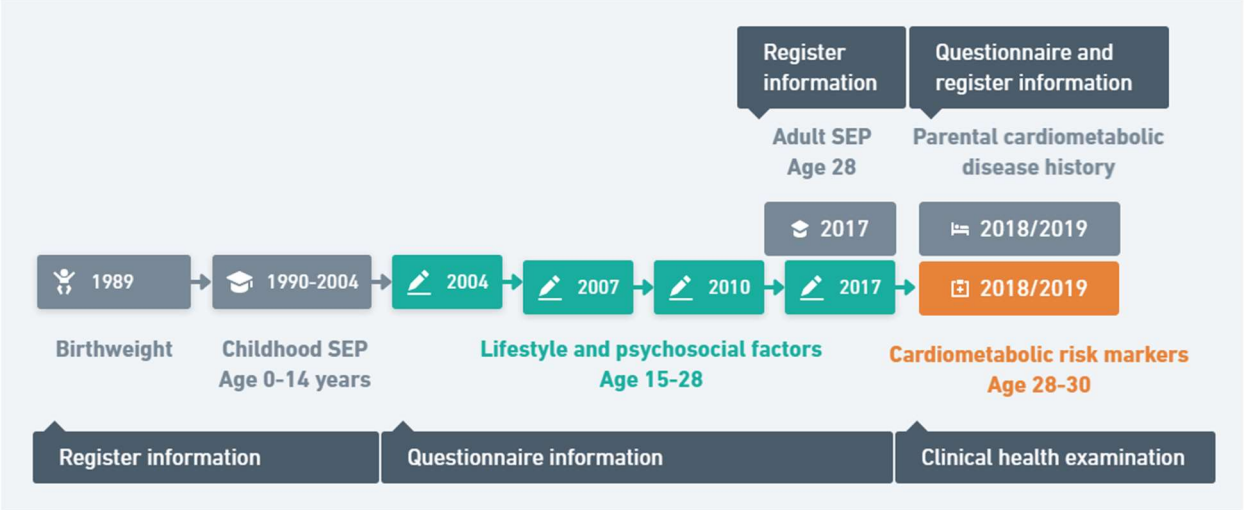
The Danish Medical Birth Register provides information about all hospital and home births in Denmark from 1973 onwards(120). In the studies summarized in this dissertation, information about the birth weight of the participants was used.

Study designs

We conducted four studies based on information from the clinical health examination of the subsample (N = 264) from the West Jutland Cohort. The information was combined with questionnaire information and population-based national register information. Study 1 was a cross-sectional study. Studies 2, 3 and 4 were prospective studies. An illustration

of the data sources and the temporal relationship of the data collection is presented in Figure 6 as a graphical timeline. Furthermore, an overview of the four studies is provided in Table 2. The variables, statistics and approvals of the studies are presented below. Details about the specific items used in the questionnaire are presented in Appendix 4 of the dissertation.

Figure 6. Graphical timeline of the data collection



SEP, Socioeconomic position

Table 2. Overview of the studies

	Study 1	Study 2	Study 3	Study 4
Topic	Cardiometabolic risk markers across strata of sex and body mass index	Life course SEP and cardiometabolic disease risk	The impact of mental health on the association between childhood SEP and cardiometabolic disease risk	Subjective social status and cardiometabolic disease risk
Study design	Cross-sectional	Prospective	Prospective	Prospective
Data sources				
Clinical health examination	√	√	√	√
Questionnaires	(√)	√	√	√
Registers	(√)	√	√	√
Variables				
Exposure	Body mass index	Childhood SEP (household income and educational level of the mother in three age periods)	Childhood SEP (educational level of the father and the mother at age 14)	Subjective social status
Outcome	A total of 24 CMR markers	Composite CMR score	Composite CMR score	Composite CMR score

Additional variables				
Sex	√	√	√	√
Parental cardiometabolic disease history	(√)	√	(√)	
Birth weight		√	√	
Adult educational level		√		√
Behavioral factors	(√)	√	(√)	√
Psychological factors			√	
Childhood SEP				√
Primary statistical analyses	Kruskal-Wallis test	Multivariable regression models and diagonal reference models	Mediation analyses using nested counterfactuals	Hierarchical multivariable regression models
Inverse probability weights		√	√	√

SEP, socioeconomic position; CMR, cardiometabolic risk. (√) *illustrates descriptive or supplementary analyses.*

Exposure variables

Body Mass Index

BMI was used as exposure variable in study 1. It was calculated from measures of height in meters (m) and weight in kilograms (kg) at the clinical health examination. The formula was BMI = kg/m^2.

Childhood household income

Childhood household income was used as exposure variable in study 2 and as covariate in study 4. The variable was obtained from The Income Statistics Register and defined as equivalized household income. Equivalized household income is a weighted variable taking the size and distribution of the family into account(121)[3]. We averaged the mean of each year when data was available for at least 3 years during the three age periods of 0–5, 6–10 and 11–15 years. In study 2, we categorized the variable into low, average and high household income at the 33.3rd and 66.6th percentiles of the entire West Jutland Cohort Study. In study 4, we used the variable as a continuous measure.

Educational level of the parents

The educational level of the parents when the participants were 14 years old was used as exposure variable in studies 2 & 3 and as covariate in study 4. The variable was obtained from the Danish Education Registers and categorized into low, middle and high. The categorization was based on years of completed education (≤10, 11–13, >13), which in

[3] Based on the OECD modified scale: The first adult is assigned a weight of 1, the subsequent adults >14 years are assigned a weight of 0.5 and children a weight of 0.3.

Denmark is approximately equivalent to completion of compulsory school, secondary education and tertiary education. In study 3, the variable was dichotomized into low and high based on the years of completed education (≤10 and >10).

Social mobility

Social mobility was used as exposure variable in study 2. The variable was defined as upward, downward or immobile when adult educational level was above, below or the same as the parental educational level.

Subjective social status (SSS)

SSS was used as exposure variable in study 4. The variable was obtained from questionnaires at ages 15 and 28 using the youth version of the MacArthur scale of Subjective Social Status (item specification available in Appendix 4). The scale ranged from 1–10, with higher values indicating higher perceived social status. We dichotomized the scale based on the sex-stratified 25th percentiles of the entire West Jutland Cohort Study population, resulting in low SSS (ladder steps 1–5) and high SSS (ladder steps 6–10) for both sexes.

Outcome variables

The outcome variables consisted of various cardiometabolic disease risk markers obtained at the clinical health examination. In study 1, 24 cardiometabolic risk markers were evaluated separately. In studies 2, 3 and 4, a cardiometabolic risk (CMR) score was calculated from nine risk markers covering four biological domains: inflammation (high-sensitive C-reactive protein (hs-CRP), interleukin-6 and fibrinogen), lipids (triglycerides and inverse values of high-density lipoprotein cholesterol), blood pressure (systolic blood

pressure and diastolic blood pressure) and glucose metabolism (glucose and insulin). The nine risk markers were standardized (inflammatory markers on the log scale) and inverse probability weights, represented by latest self-reported BMI group were applied. The standardized scores were generated for each sex separately and summarized within each biological domain. The mean values of the four domains were then summarized and standardized to create the CMR score. Two participants with diabetes mellitus type 1 were excluded from the glucose metabolism domain but included in the overall CMR score. One participant was not fasting at the clinical health examination and obtained the median value of same sex glucose and insulin.

Additional variables

Sex

Information about sex was obtained from The Danish Civil Registration System and defined as the biological sex of the participant at birth.

Parental cardiometabolic disease history

Information about parental cardiometabolic disease history was obtained from the additional questionnaire sent to the participants prior to the day of the health examination and supplemented with information from The Danish National Patient Register. Appendix 5 presents the ICD-10 codes of the diagnoses used in this dissertation. The variable was divided into cardiovascular and metabolic parental disease history and dichotomized into none and some.

Birth weight

Birth weight was derived from The Danish Medical Birth Register. Due to approximately 4% missing values in the register, we supplemented the data with information from parental questionnaires in 2004 when the child was 15 years old. Birth weight was used as a categorical measure based on national guidelines of high, normal and low (≥4500, 2500–4500 and <2500 gram) in study 2 and as a continuous measure in study 3.

Educational level of the participant

The educational level of the participant was obtained from The Danish Education Registers and categorized into low, middle and high based on the years of completed education (≤10, 11–13, >13) at age 28.

Behavioral factors

Behavioral factors included physical activity and smoking. Information about physical activity was obtained from questionnaires at ages 15, 18, 21 and 28. The participants were asked "How many hours a week during leisure time do you usually exercise or play sports where you are out of breath or sweating?" Original categories were: None, ½ hour, 1 h, 2–3 h, 4–6 h, and 7 h or more (at age 28: 7–10 h and 11 h or more). In study 1, the variable was divided into three categories of ≈0–0.5 h, ≈1–3 h and ≥4 h each week from information at age 28. In study 2, a score ranging from 0–4 was constructed. The score was generated from the number of age points each participant attained the recommended level of physical activity for Danish adolescents (1 hour/day) and adults (30 minutes/day)(122). Higher scores indicated higher levels of physical activity. If the participant was missing one response, this was replaced with the mean value of the three available responses. In study 4, the variable was categorized as the original categories

from the questionnaires at ages 15 and 28. Information about smoking was obtained from the questionnaire at age 15 and from the additional questionnaire received prior to the health examination (at ages 28–30). In study 2, the variable was categorized into current, former or never smoker. In studies 1 and 4, the variable was dichotomized into never or ever (current and former).

Psychological factors

Information about psychological factors was obtained from questionnaires at ages 15, 18, 21 and 28. The psychological factors included four symptom scales evaluating sense of coherence (meaningfulness), self-esteem, depressive symptoms and perceived stress.

Sense of Coherence

Sense of coherence is a multidimensional construct believed to capture the ability of an individual to understand, manage and make sense of various life situations in order to cope efficiently(123). The original questionnaire used to measure sense of coherence was developed by Antonovsky and consisted of 29 items, creating a summed score measuring the three components: comprehensibility, manageability and meaningfulness(124, 125). Later the 13-item score and a revised version for children was developed(125, 126). In the current study, we used a revised 4-item short version relating to meaningfulness.

Self-esteem

Most research concerning self-esteem is based on Rosenberg's self-esteem scale. According to Rosenberg, self-esteem is defined as "*the evaluation which the individual makes and customarily maintains with regard to himself or herself: it expresses an attitude of approval or disapproval toward oneself*"(127). This construct includes three

major topics: 1. Reflected appraisal (the individual's interpretation of how others view them), 2. Social comparison (judgement of oneself by comparison with others), and 3. Self-attributions (conclusions about oneself based on own actions, including successes and failures). In the current study, we used a 6-item short version of the original Rosenberg 10-item scale(128).

Depressive symptoms

Depression is common and many cases initiate or establish at young age(129, 130). Furthermore, depressive symptoms without reaching the threshold for diagnosis are associated with poor health outcomes(131). In the current study, we used a 4-item short version of the Center for Epidemiological Studies Depression Scale for children, adolescents and young adults (CES-DC)(132). The scale measures depressive symptoms within the last week and is a general measure of psychopathology capturing subtle distinctions between individuals rather than a measure of depressive disorders(132).

Perceived stress

Stress was initially defined in 1936 as the adaptive response to either psychological or physical threats(133). Stress was defined as an independent response in addition to the reaction toward the source creating the threat. Psychological stress occurs when emotional or social demands exceed the adaptive capacity of an individual and thus induce the physiological stress response(134). Perceived stress is the individual's subjective measure of appraised stress. In the current study, we used a Danish 4-item version of Cohen's original 14-item Perceived Stress Scale at ages 15, 18 and 21, and a 10-item version at age 28(135).

To evaluate the overall and accumulated influence of the psychological factors, we generated a global score from all four symptom scales across all four age points. The score was created for each sex separately based on responses from the entire West Jutland Cohort Study. This was done in three steps. Initially, each psychological scale was standardized. Secondly, the individual mean score of the four scales of each year was calculated. Finally, the mean score across all four age points was calculated. Participants were included if they had responded to at least two psychological factors at least two times. Higher scores indicated poorer mental health. As a sense of coherence (meaningfulness) and self-esteem are inversely related to depressive symptoms and perceived stress, these values were multiplied by -1 prior to generating the global score.

Statistical analyses

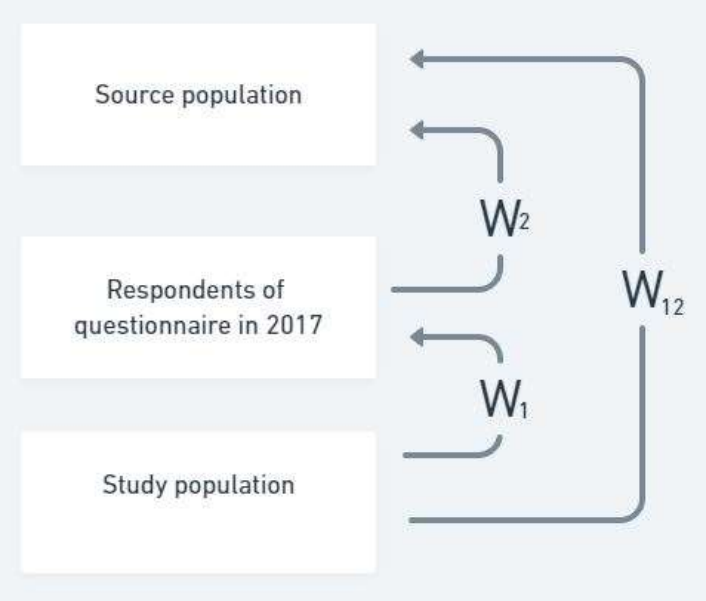
All statistical analyses reported in this dissertation were performed with Stata software version 16.0 and 16.1 (STATA corporation, College Station, Texas, USA). In all studies, descriptive data were presented as absolute numbers (percentages) for categorical variables and mean (standard deviation) or median (interquartile ranges) for continuous variables.

Probability weights

To compensate for the unequal probability of participation in the clinical health examination, we calculated probability weights based on the inverse probability of being sampled by BMI group and sex. I will denote this probability P_1. The probability weight is

given by $W_1 = \frac{1}{P_1}$. W_1 was used in studies 2–4[4]. To further compensate for imperfections due to non-respondents of the questionnaire in 2017, we calculated probability weights based on childhood SEP (educational level of the mother) and sex that were available from registers. I will denote this probability P_2. The overall probability weight of participation in the clinical health examination is given by $W_{12} = \frac{1}{\mathrm{P1} \times \mathrm{P2}}$ (Figure 7). We repeated the main analyses of studies 2–4 including W_{12}. The results of the repeated analyses are presented in Appendix 7–Appendix 9 of the dissertation.

Figure 7. Overview of the inverse probability weights used in study 2-4.



Study 1 Kruskal-Wallis test

To evaluate the risk marker levels across the three BMI groups for each sex, we used Kruskal-Wallis one-way analysis of variance. The Kruskal-Wallis test is a non-parametric method based on ranks. Comparing only two groups, the test is equivalent to the

[4] Since we stratified on BMI group and sex in study 1, we did not apply probability weights in this study.

Wilcoxon rank sum test. We conducted additional analyses evaluating the Spearman correlation between continuous measures of BMI and the cardiometabolic risk markers applying the Bonferroni correction.

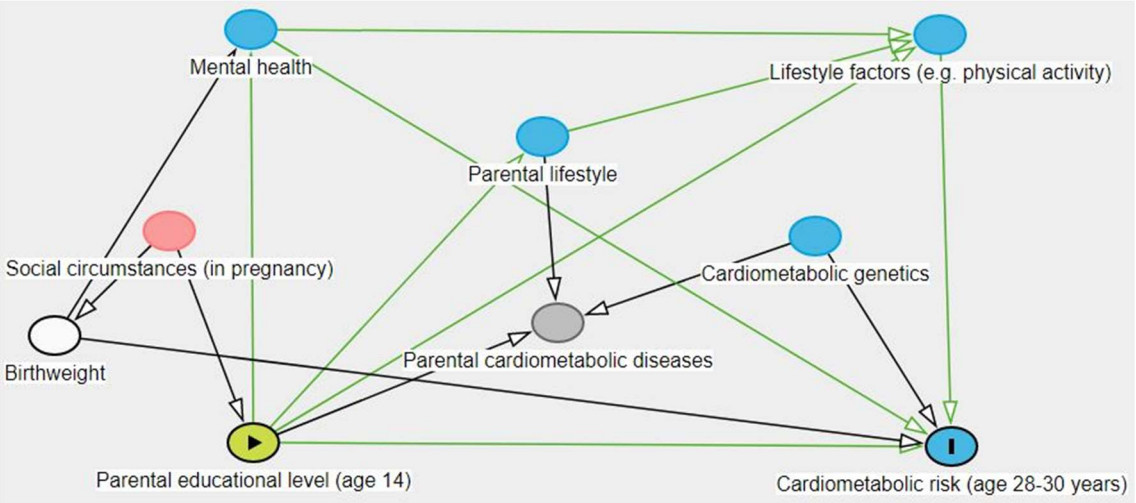
Study 2 Multivariable regression models and diagonal reference models

To evaluate the association between childhood SEP and the CMR score by the latent effects, the cumulative and the pathway models, we used multivariable regression models. The models were checked using diagnostic plots of the residuals. To evaluate the distinct association between social mobility and the CMR score, we used diagonal reference models (DRM). Conventional linear regression models, including childhood SEP, adult SEP and mobility effects, might cause problems due to multi-collinearity since the mobility per definition is measured by the difference between childhood and adult SEP. DRM is specifically designed to disentangle social mobility in order to respect that outcome (the CMR score) may be affected by both the origin (childhood SEP), destination (adult SEP) and the mobility itself(136). All analyses were performed unadjusted as well as adjusted for birth weight, sex and parental cardiometabolic disease history.

Study 3 Causal inference and nested counterfactuals

To quantify the mediating impact of psychological factors on the association between childhood SEP and the CMR score, we conducted analyses within the causal inference framework using a counterfactual-based mediation model. Potential confounders were identified by a directed acyclic graph (DAG) constructed from subject-matter knowledge and prior literature. A simplified DAG is presented in Figure 8.

Figure 8. Simplified DAG of assumed structures in study 3 (dagitty.net)



We estimated the effects by changing childhood SEP from high to low in multiple steps using nested counterfactuals as described by VanderWeele(137). Further description of the applied statistics is available in the embedded paper 3. We conducted supplementary analyses including physical activity, parental cardiometabolic disease history and parental psychiatric disorders as confounders.

Study 4 Multivariable regression models

To evaluate the association between SSS and the CMR score, we performed sex-stratified multivariable regression models in a hierarchical manner. The models were checked by diagnostic plots of the residuals. Model 1 evaluated the crude estimates. Model 2 included physical activity and smoking status. Model 3 included physical activity, smoking status and childhood SEP. Model 4 (only SSS measured at age 28) included physical activity, smoking status, childhood SEP and adulthood SEP. We conducted additional analyses dichotomizing the exposure variable SSS into low (steps 1–4) and high (steps 5–10) as has been done in previous literature(36).

Approvals

The overall study was approved by the Danish Data Protection Agency (by reporting the study to the local regional authority with data responsibility) and the National Committee on Health Research Ethics (no: 1-10-72-400-17). Furthermore, participants signed a statement of informed consent prior to the health examination.

4

Chapter 4, Results in summary

The following chapter summarizes the main findings from studies 1–4. Detailed descriptions of the results are available in the embedded papers. Findings presented below are reproduced from the data presented in the papers and supplemented with additional analyses.

Characteristics of the population

Educational level of the mother and adult educational level of the source population, among respondents of the questionnaire in 2017 and among participants in the clinical health examination, are presented for each sex separately in Figure 9 and Figure 10. Furthermore, the figures include parental cardiometabolic disease history from registers, strata of BMI, smoking habits and level of physical activity from self-reported measures in the questionnaire in 2017. As can be seen, some differences between the source population, respondents and study participants exist in both sexes. Overall, more in the groups with a low SEP in childhood and adulthood were non-respondents. There are minor differences across BMI-stratified SEP, parental disease history and self-reported lifestyle factors comparing respondents in 2017 and study participants in the clinical health examination.

Figure 9. Population characteristics, men

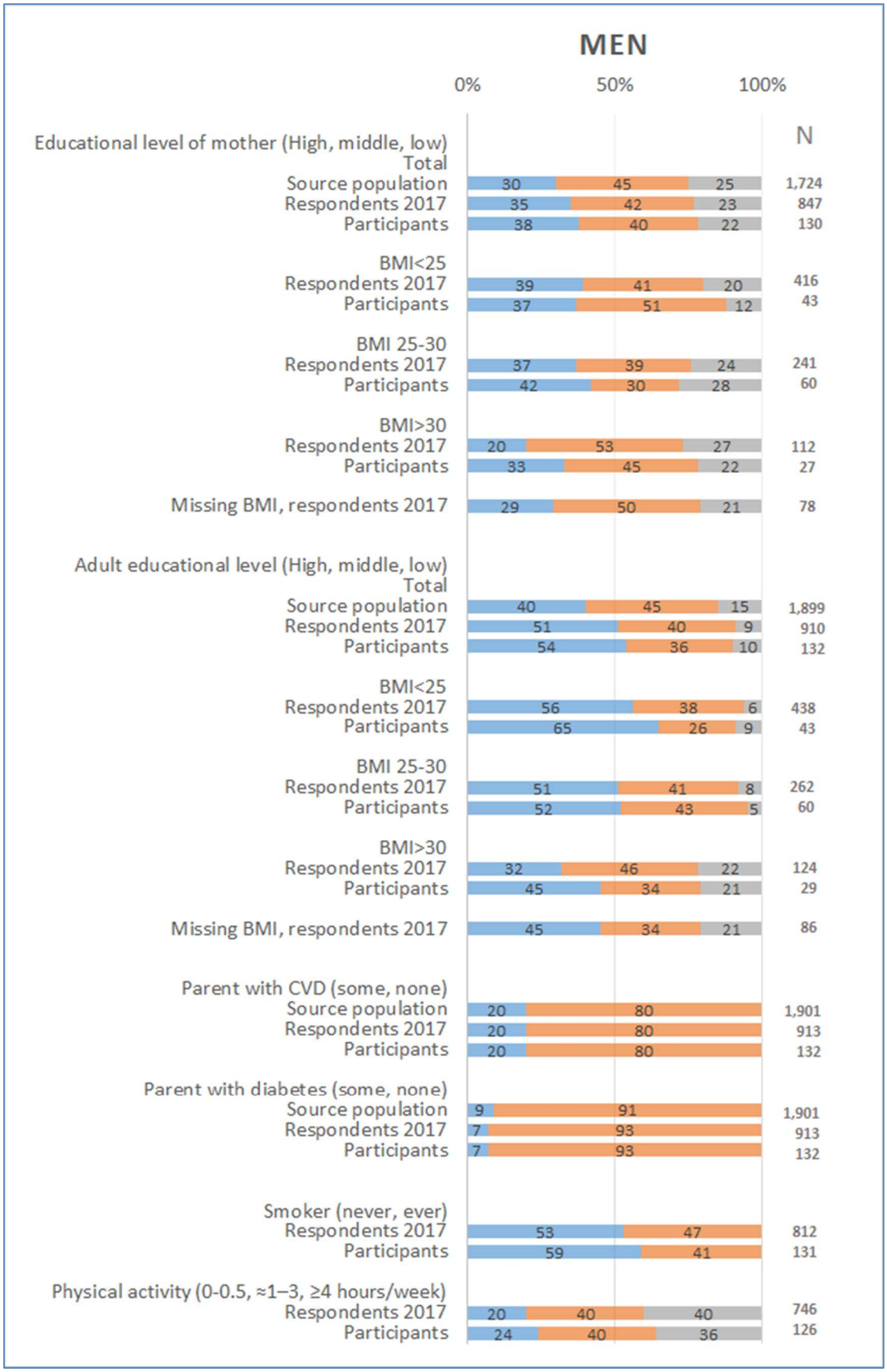
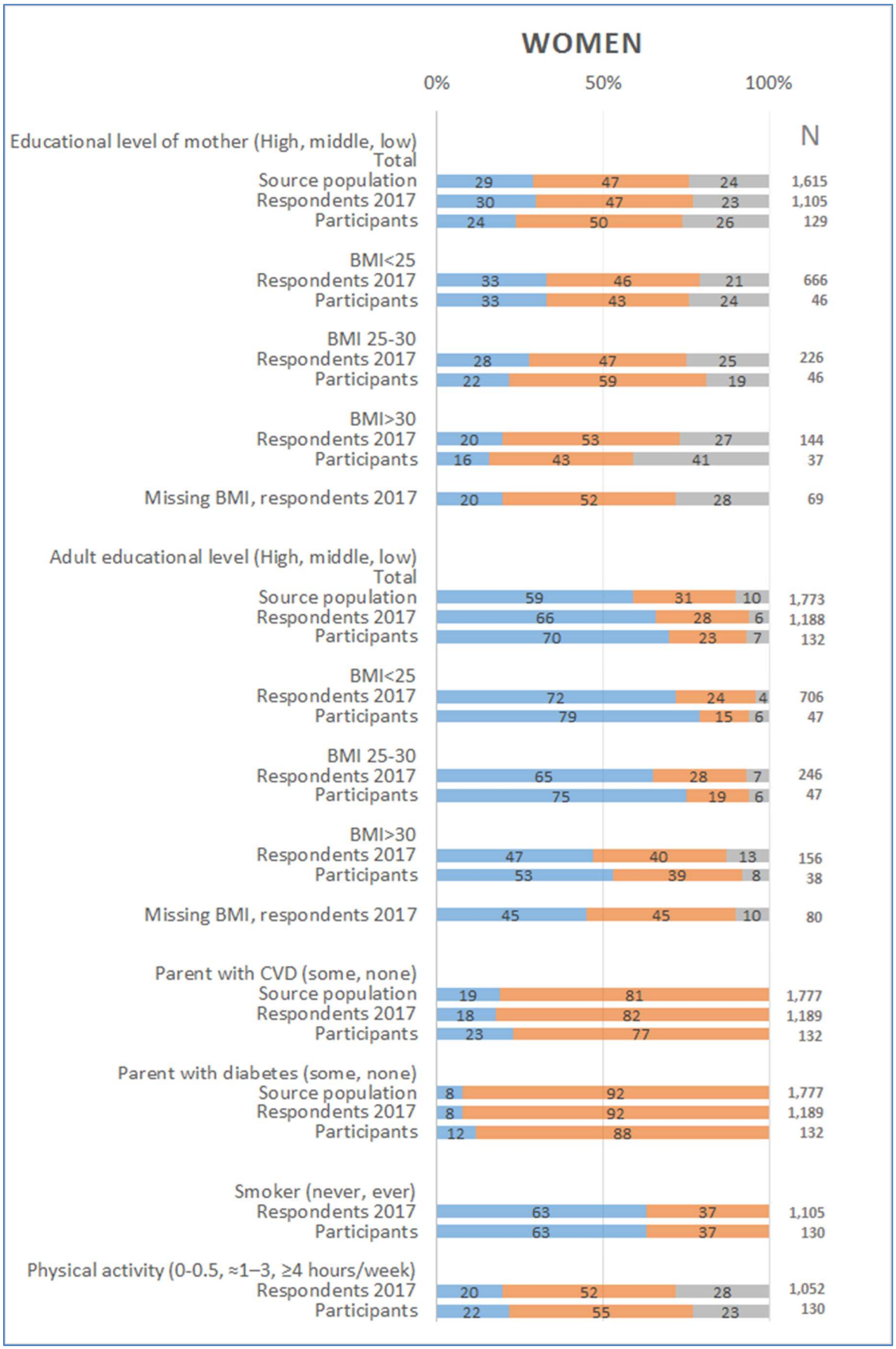


Figure 10. Population characteristics, women



Study 1

Cardiometabolic risk markers across strata of sex and body mass index in young adults

A total of 24 different cardiometabolic risk markers are presented in strata of BMI and sex in paper 1(115). No clinically significant coronary artery calcification (CAC) was detected in any of the participants, evaluated by computed tomography. Furthermore, none of the participants reached the thresholds for pre-diabetes measured by fasting glucose or HbA1c. A total of 35 participants, corresponding 13%, fulfilled the criteria for metabolic syndrome evaluated according to the International Diabetes Federation definition. Figure 11 and Figure 12 visualize the relationship between continuous measures of the risk markers by heat maps for each sex separately. Furthermore, sex-stratified correlations between BMI and the cardiometabolic risk markers with Bonferroni-adjusted p-values are presented in Appendix 6. We found weak to strong correlations between BMI and multiple measured risk markers at ages 28–30 years. Noticeably, some of the risk markers that are often used in the clinical setting, e.g. systolic blood pressure (SBP), total cholesterol (TC), LDL-cholesterol (LDL-C) and HbA1c, showed minor correlations with BMI, whereas insulin and markers of inflammation, e.g. hs-CRP and fibrinogen, showed greater correlation with BMI.

Figure 11. Heat map of correlation between cardiometabolic risk markers for men, study 1

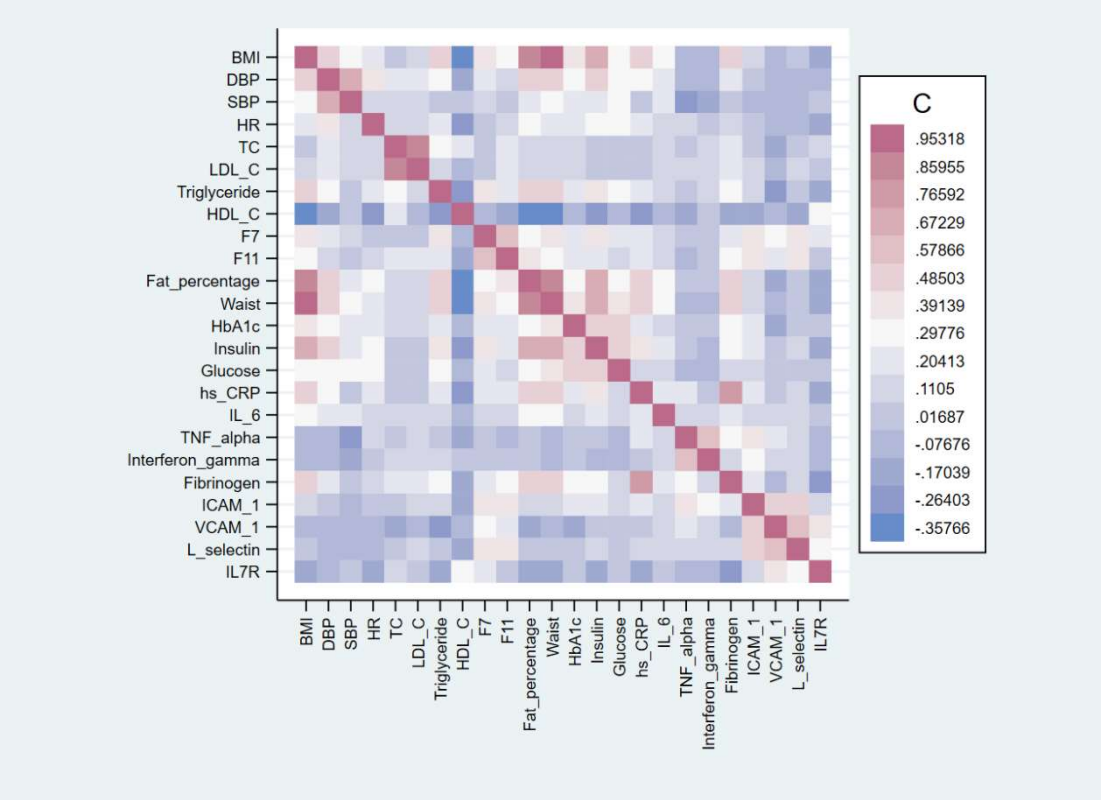
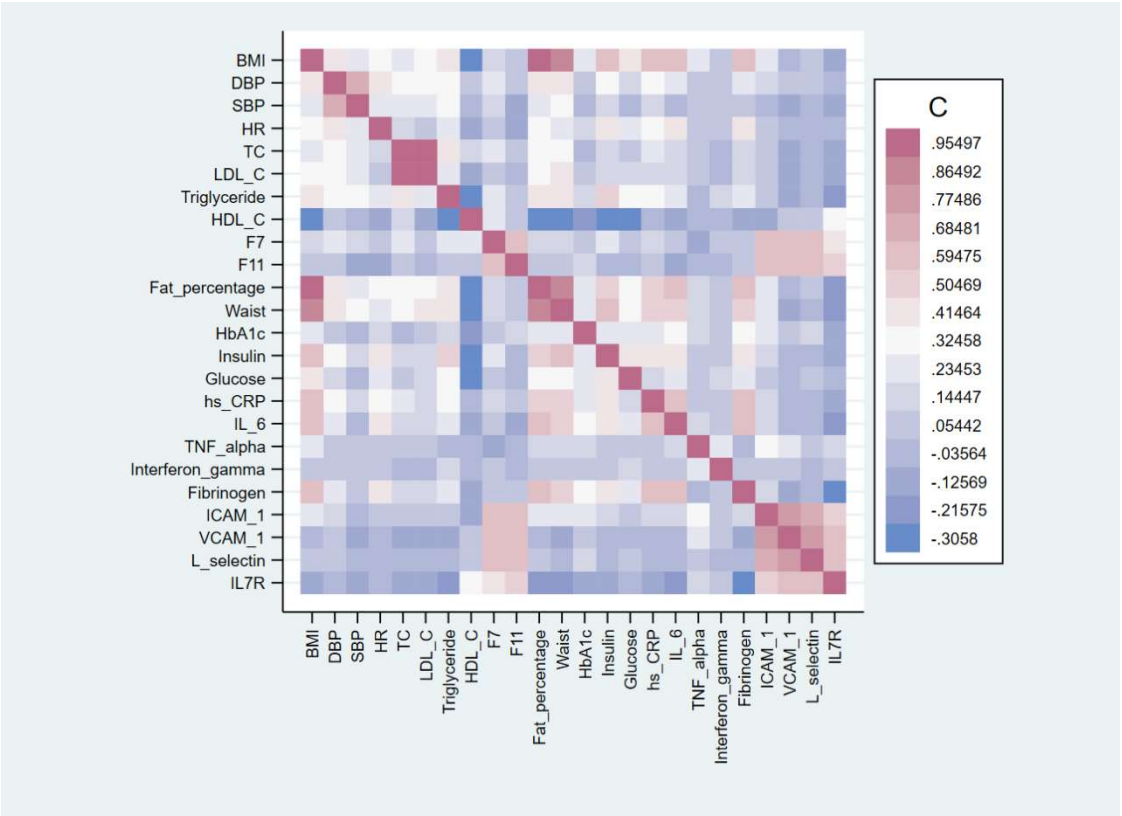


Figure 12. Heat map of correlation between cardiometabolic risk markers for women, study 1



Study 2

Life course evaluation of childhood socioeconomic position and cardiometabolic risk in young adults

Unadjusted and adjusted analyses evaluating the latent effects model, the pathway model, the social mobility model and the cumulative model by household income and educational level of the mother are presented in paper 2. Table 3 presents the adjusted results evaluating educational level of the mother as exposure measure. We found higher cardiometabolic risk score among those whose mothers had low educational level compared to those with an average and high educational level. We found no significant "latent effect" on evaluation of three periods in childhood, and no specific association between intergenerational social mobility and the cardiometabolic risk score. However, we found the weight of destination to be greater than that of origin (74% vs. 26%, standard error 0.15) evaluated by DRM. The weight is a measure between 0 and 1, and a weight of 50% would imply that the origin and destination are equally important. We found support for the pathway model and the cumulative model. We found no association between household income and the cardiometabolic risk score evaluated by any of the life course models. Supplementary analyses evaluating household income as a continuous measure did not change the results. The main results remained essentially unchanged after applying W_{12} to the adjusted analyses, except that upward mobility was marginally significantly associated with decreased cardiometabolic disease risk compared to immobile individuals (Appendix 7).

Table 3. The association between educational level of the mother and cardiometabolic risk evaluated by four life course models, study 2

	Adjusted cardiometabolic risk score (95% confidence interval)			
		Educational level of the mother		
	N	**High**	**Average**	**Low**
The latent effects model*				
Early childhood	*246*	**Ref**	-0.2 (-0.5;0.1)	0.2 (-0.1;0.6)
Middle childhood	*246*	**Ref**	-0.2 (-0.5;0.1)	0.3 (-0.1;0.6)
Late childhood	*249*	**Ref**	-0.2 (-0.5;0.1)	0.3 (-0.1;0.6)
The pathway model				
Prior to adjustment for lifestyle and adult SEP	*249*	**Ref**	-0.1 (-0.4;0.2)	**0.4 (0.1;0.7)**
After adjustment for lifestyle and adult SEP	*227*	**Ref**	-0.2 (-0.5;0.1)	0.3 (-0.1;0.6)
The social mobility model	*249*			
Separate upward mobility coefficient		-0.3 (-0.8;0.2)		
Separate downward mobility coefficient		-0.1 (-0.6;0.5)		
The cumulative model	*246*			
Regression coefficient		**0.1 (0.0;0.1)**		

*SEP, socioeconomic position. * Adjusted for adult SEP.*

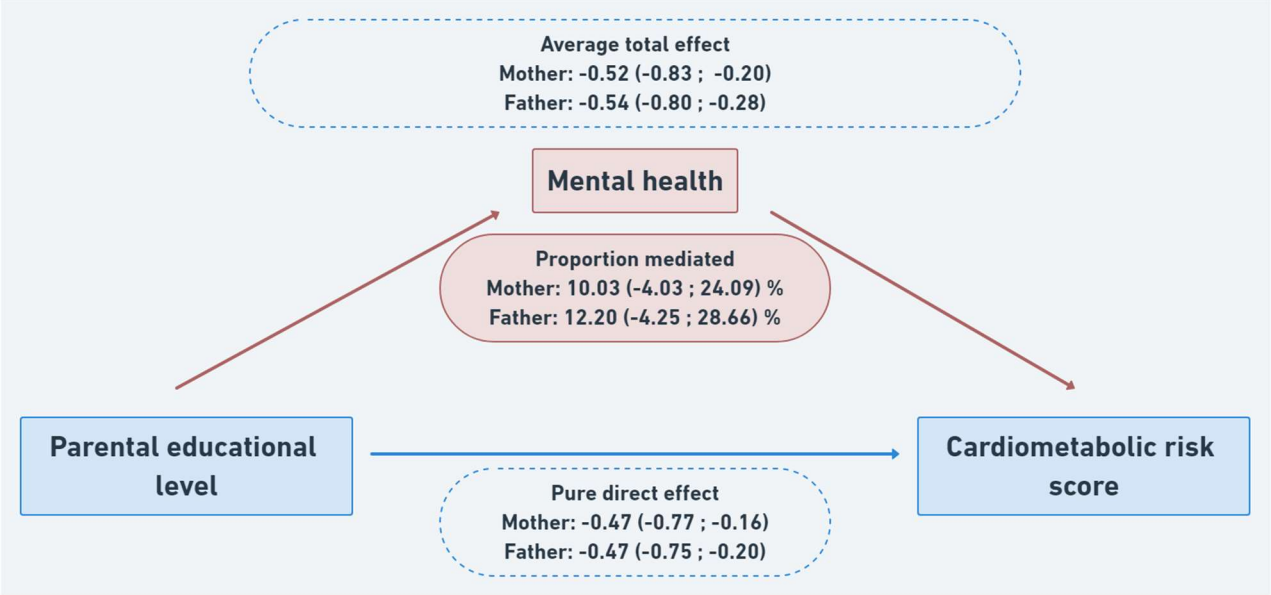
The latent effects model:	Supported if the association remains after adjustment for adult SEP
The pathway model:	*Supported if the inverse association attenuates after adjustment for lifestyle and adult SEP*
The social mobility model:	*Supported if systematic differences remain comparing social mobile and immobile individuals*
The cumulative model:	*Supported if SEP summarized throughout the life course (the three periods in the latent effects model + adult SEP) is associated with the cardiometabolic risk score*

Study 3

The impact of mental health on the association between childhood socioeconomic position and cardiometabolic risk in young adults

We found inverse associations between educational level of either parent and the cardiometabolic risk score. In causal mediation analyses, we found that 10 (-4; 24)% and 12 (-4; 29)% of the association were mediated by accumulated mental health, evaluating the educational level of the mother and the father, respectively(Figure 13).

Figure 13. Results from counterfactual mediation analyses, study 3



The average total effect is defined as the hypothetical contrast of the CMR score had everyone been exposed versus had no one been exposed. The pure direct effect is explained by other factors than mental health. Results are presented with 95% bootstrap confidence intervals.

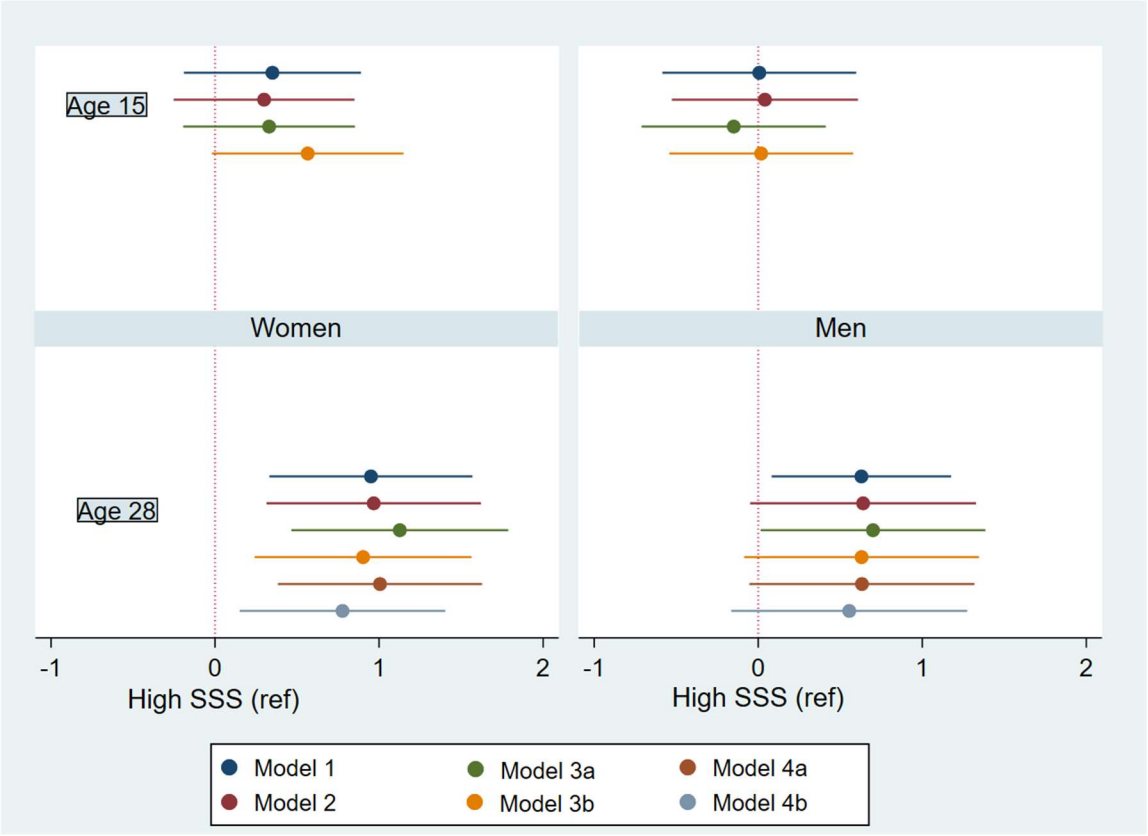
Evaluating either of the four symptom scales individually attenuated the proportion mediated. The results remained largely unchanged applying W_{12} to the analyses (Appendix 8). In two supplementary analyses, we adjusted for physical activity and parental cardiometabolic disease history. Adjusting for physical activity reduced the proportion mediated by mental health to 4 (-12; 21)% and 7 (-16; 29)% evaluating the educational level of the mother and father, respectively. Adjusting for parental cardiometabolic disease history reduced the proportion mediated by mental health to 8 (-16; 32)% and 5 (-8; 18)% evaluating the educational level of the mother and father, respectively.

Study 4

The association between subjective social status in adolescence and young adulthood and cardiometabolic risk in young adults

There was a rather weak correlation between SSS at age 15 and age 28 (Spearman's rho = 0.20 for women and 0.19 for men). Figure 14 presents the main findings from the hierarchical regression analyses.

Figure 14. Subjective social status and the cardiometabolic risk score in young adulthood, study 4



SSS, subjective social status. All estimates are presented with 95% confidence intervals.

Model 1: *Crude estimates of low SSS (higher values indicate higher cardiometabolic risk)*

Model 2: *Model 1 + smoking and physical activity at ages 15 and 28, respectively*

Model 3a: *Model 2 + educational level of the mother. Model 4a: Model 3a + adult educational level*

Model 3b: *Model 2 + childhood household income. Model 4b: Model 3b + adult educational level*

Further statistical detail is presented in the embedded paper 4. Girls at age 15 and men and women at age 28 indicating low SSS, on average, had higher values of the cardiometabolic risk score. This association was statistically significant in both sexes at age 28 in the crude model and for women in all models. Among boys at age 15, we found no association between SSS and the cardiometabolic risk score at ages 28–30. Adjusting for childhood SEP and health behavior did not change the estimates markedly. Adding adult SEP at age 28 resulted in a minor attenuation in women. In men, the confidence intervals became wider but the estimates did not change markedly. The results remained largely unchanged applying W_{12} to the adjusted analyses (Appendix 9). Additional analyses dichotomizing the exposure variable at ladder step 4 are presented in Appendix 10. Changing the cut-off did not change the overall conclusions. However, the associations between SSS and the cardiometabolic risk score in women were stronger compared to the original findings. Evaluating SSS as a continuous measure was not possible due to violation of the assumptions behind linear regression analyses assessed by post estimation plots of the residuals.

5

Chapter 5, Methodological considerations

Design of studies

Study 1 was a cross-sectional study. The exposure, BMI, was ascertained at the same time as the outcome measures of 24 cardiometabolic risk markers. A limitation of this study design was the limited potential causal interpretation of the relationship between exposure and outcome. Furthermore, we did not take into account the duration of the exposure, e.g. years with elevated BMI or different BMI trajectories. Study 1 was intended to be a pure description of the distribution of biomarkers across strata of sex and BMI and a description of the procedures underlying the clinical health examination. Studies 2, 3 and 4 were prospective studies with a clear temporal ordering of exposure, mediators and outcome. This allowed investigation of potential causal inferences of the associations. Crimmins et al. found that differences in measures of biology across SEP strata were evident from the age of 20; however, at ages above 70 the differences seem to vanish(54). Strengths of investigating social inequality in young adulthood prior to symptoms and manifest cardiometabolic diseases include a decreased risk of differences in health seeking behaviors, health care quality, treatment adherence and survival bias, which might be difficult to disentangle in studies of social inequality among older populations(98). Limitations of the age group investigated relate to the uncertainty of translating an increased cardiometabolic risk into later manifest disease, morbidity and mortality. The risk markers are evaluated as surrogate measures of disease risk, and we do not know who eventually get the diseases.

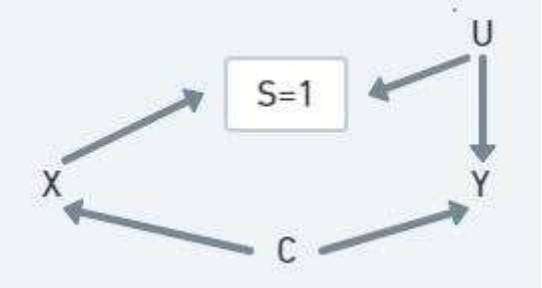
Random error

We aimed for a heterogeneous study population to allow for measures of association in a relatively small sample rather than an (utopian) attempt to make the study population representative of the source population. However, a small sample size increases the risk of random error and reduces statistical precision of the estimates(138). We quantified the precision of our estimates with 95% confidence intervals and p-values. Using p-values is much debated and rather controversial in some scientific arenas(139). P-values evaluate the null hypothesis (statistical significance vs. insignificance), are affected by the sample size and do not evaluate the clinical significance of the association. We agree that any specific p-value should never stand alone. However, in the studies of this dissertation, we used p-values to supplement the interpretation of the estimates together with confidence intervals. We also recognize "statistical insignificant" results and assess the overall tendencies in the data irrespective of the p-values.

Selection bias

The risk of differences between the study population and the source population could lead to bias of the estimates. Selection bias can arise if selection is related to both exposure status and outcome status, thereby altering a true association or inducing an association(138). Using DAG terminology, selection bias is equivalent to collider stratification bias. An example of selection bias is visualized by a DAG in Figure 15. As depicted in the DAG, conditioning on the collider S = 1 opens the path $X \rightarrow [S = 1] \leftarrow U \rightarrow Y$, thereby inducing a non-causal association between X and Y.

Figure 15. Directed Acyclic Graph illustrating selection bias



X: exposure, C: measured confounder(s), Y: outcome, U: unmeasured co-variates, S=1: selection into the study. The box around S=1 indicates conditioning.

Selection bias is considered a threat to the validity of most cohort studies and can arise from non-participation/non-response, loss to follow-up or inclusion criteria. Overall, the response rates of the questionnaires in the West Jutland Cohort study were relatively high (57–83%). However, as shown in Figure 9 and Figure 10 of this dissertation, and in a former study from the West Jutland Cohort Study, non-response to the questionnaires was associated with lower childhood SEP and male sex(140). Additionally, as a result of inclusion according to BMI and sex in the clinical health examination, the study population differs from questionnaire respondents and the source population. The use of probability weights reduces the risk of selection bias from non-response and sampling based on inclusion criteria. The re-weighting is intended to generate a pseudo-population that, on average, mimics the background population. The analyses in papers 2–4 were conducted with inverse probability weights, W_1, taking the inclusion by sex and BMI into account and thereby mimicking the respondents of the 2017 questionnaire. Applying the overall inverse probability, $W_{12,}$ did not change the findings of the studies. However, it is important to recognize that the weights are only valid if the respondents and participants truly represent the non-respondents and non-participants of each stratum of factors used

to generate the probabilities. This is potentially not the case, and some selection bias might remain that cannot be quantified. Consequently, it remains important to supplement this by speculating qualitatively in what direction selection could have affected the estimates. Thus if non-response is associated with low childhood SEP and this selection is further associated with increased cardiometabolic disease risk, the studies would be subject to selection bias that most likely would lead toward the null. Detailed discussions of potential selection bias for each study are presented in the embedded papers. Overall, we believe the findings of the studies in this dissertation are little biased by selection. However, we cannot disregard the risk and speculate that the direction of a potential bias would lead to underestimation of the associations investigated in studies 2–4.

Information bias

Information about exposure, confounders, mediators and outcome may be recorded or measured inaccurately. Information bias includes recall bias, observer bias and measurement error that lead to misclassification. Misclassification of the variables can be either non-differential (random and equally distributed across study groups) or differential (different probability of inaccuracy across study groups)(138). In the current study, we used different data sources to gain information: questionnaires, registers and clinical measurements. Overall, the use of different data sources is seen as a strength because it decreases the risk of common-method bias(141). However, risk of information bias is present in varying degree in each data source, i.e. over- and underreporting in questionnaires, missing information in registers and inaccurate clinical measurements. In

the following sections, considerations are presented regarding misclassification of the key data used in this dissertation.

Misclassification of exposure

Traditionally, non-differential measurement error of an exposure is expected to lead toward the null, thus underestimating a true association(138). In contrast, differential measurement error can lead in either direction and result in either overestimation or underestimation of an association. The exposure, BMI, in study 1 was calculated from measures of height and weight by trained nurses using calibrated equipment and standardized methods. We consider the accuracy of these measurements to be high, with little risk of misclassification. The categorization might bias the results toward the null. However, the analyses evaluating BMI as a continuous measure did not change the overall findings. The exposures, parental educational level and household income in studies 2 and 3 were derived from population-based national registers with high coverage. This eliminates the risk of recall bias and reduces the risk of misclassification. We consider the validity of the register-based exposures to be high; however, some misclassification might remain due to categorization and averaging across years. We expect this to be limited and, in any case, non-differential. The exposure, SSS, in study 4 was derived from questionnaires. The questionnaire information is self-reported, which might cause information bias due to either over- or underreporting and difficulties interpreting the specific item, especially at age 15. Furthermore, the measure was originally a continuous measure. Previous studies use various categorizations, and no consensus as to cut-off level exists. We dichotomized the variable at the 25th percentile of the West Jutland Cohort Study population. This was a rather pragmatic choice.

Consequently, we performed a sensitivity analysis with a cut-off at ladder step 4 to test whether the categorization seemed reasonable. This strengthened the estimates compared to the initial analyses. As the trend was in the same direction and the main conclusions remained unaffected, we consider the cut-off to be acceptable. We cannot rule out some information bias, and non-differential misclassification of the measure at age 15 might partly explain the limited association at this age point.

Misclassification of outcome

All outcome measures consisted of information from the clinical health examination. We used standardized procedures to gain information, and the study nurses were instructed by written and oral information. We evaluated the variability of measures across nurses and time period of measurement. We found major inter-observer and time-varying differences on evaluation of the values from the ultrasound measurements of the carotid intima-media thickness. All stored ultrasound images were afterwards assessed by the PhD student. Due to a high degree of measurement error and inconsistency, these measurements were excluded from the studies. No inter-observer or time-varying differences were observed concerning the remaining outcome measures. The blood samples were centrifuged at the study site, placed in labeled tubes and stored at –80 degrees. Samples remained stored until batch analysis when inclusion ended to prevent differences in calibration of the equipment used for the biochemical analyses. However, storage might have affected the stability of some of the samples(142). We expect this error to be minor and non-differential.

We used a composite outcome measure in studies 2–4. Initially, we wanted to define clusters of cardiometabolic disease risk by data-driven K-means cluster algorithm of the

risk markers. Prior to clustering, we evaluated this method empirically by the "elbow-method" specifying the number of clusters, k, as two, three and four. The sex-stratified graphs were visually inspected, and since there was no distinct "elbow" decreasing the within-cluster-sum of squares, we abandoned this approach and constructed the continuous CMR score. This approach moves beyond the traditional practice of high- versus low-risk individuals and considers disease risk as a continuum. The interpretation and dissemination of the results from a population-specific continuous score may be more difficult. However, a continuous outcome measure is less error prone than a dichotomous or categorical outcome measure(143). We conducted sensitivity analyses including other risk markers in the outcome measure (body-fat percentage and HbA1c). This did not change the overall findings, which induces some confidence regarding the robustness of the composite measure. However, we cannot exclude misclassification, which we expect would be non-differential and dilute the associations investigated in the studies.

Misclassification of confounders and mediators

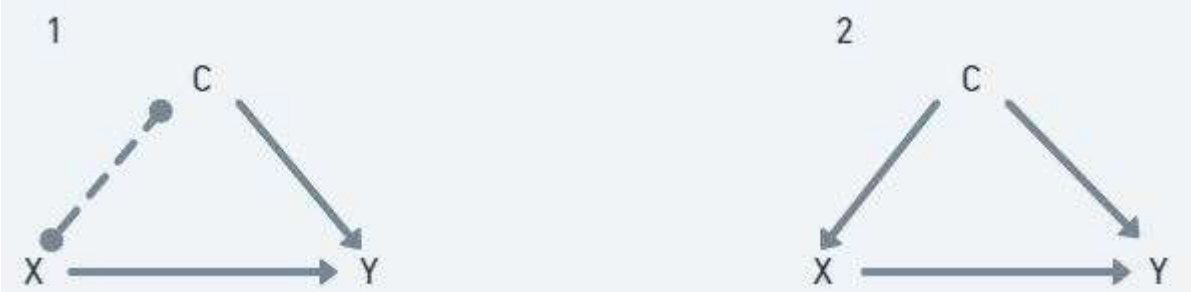
Overall, non-differential misclassification of confounders may bias the association of interest in either direction(138). We consider the validity of the register-based confounders to be high. However, the categorization of the variables might lead to misclassification and thus residual confounding. Confounding is described in more detail in the section below. Information about physical activity and smoking status was obtained from questionnaires. These measures might be subject to over- or underreporting, recall bias as well as misclassification due to categorization. Furthermore, physical activity might be unstable over time and therefore questions about it may be difficult for the

participant to respond to accurately. The mediator in study 3 was a composite score of four symptom scales derived from questionnaire information. Since subclinical measures of mental health are subjective in nature, it seems reasonable to evaluate by self-reporting. However, some concerns need to be addressed. Firstly, there is a risk of interpretation difficulties and over- or underreporting of each symptom scale by the respondent. Secondly, measures of mental health may possibly vary over time and consequently depend on time of measurement. Thirdly, the use of abbreviated scales could result in loss of information and thus inaccurate measures. All of the abovementioned concerns can lead to misclassification that we expect would be non-differential. We created the accumulated composite score from different measures of mental health across different age points. This was done in an attempt to overcome some of the concerns mentioned above, to induce robustness to the measure and capture the overall mental health of the participant. We conducted additional analyses, evaluating each of the symptom scales individually. All findings were in the same direction; however, the proportion mediated in the association between childhood SEP and cardiometabolic disease risk was attenuated compared to the composite score. VanderWeele et al. showed that non-differential misclassification of a continuous mediator will bias the indirect effect toward the null, thus decreasing the proportion mediated(144). Despite the effort to create a more robust measure of mental health, some non-differential measurement error most likely remains, and we cannot exclude that the proportion mediated in our study is underestimated.

Confounding

Confounding refers to a mixing of effects and is a critical factor in epidemiology. The historical definition of a confounder is any third variable that is a risk factor for the outcome, related to the exposure of interest and is not an intermediate of the causal path between the exposure and outcome (Figure 16, panel 1)(138). Confounding in DAG terminology refers to a variable that is a common cause of the exposure and outcome (Figure 16, panel 2).

Figure 16. Confounding structures by historical definition (1) and using DAG-terminology (2)



X, exposure, C, confounder, Y, outcome.

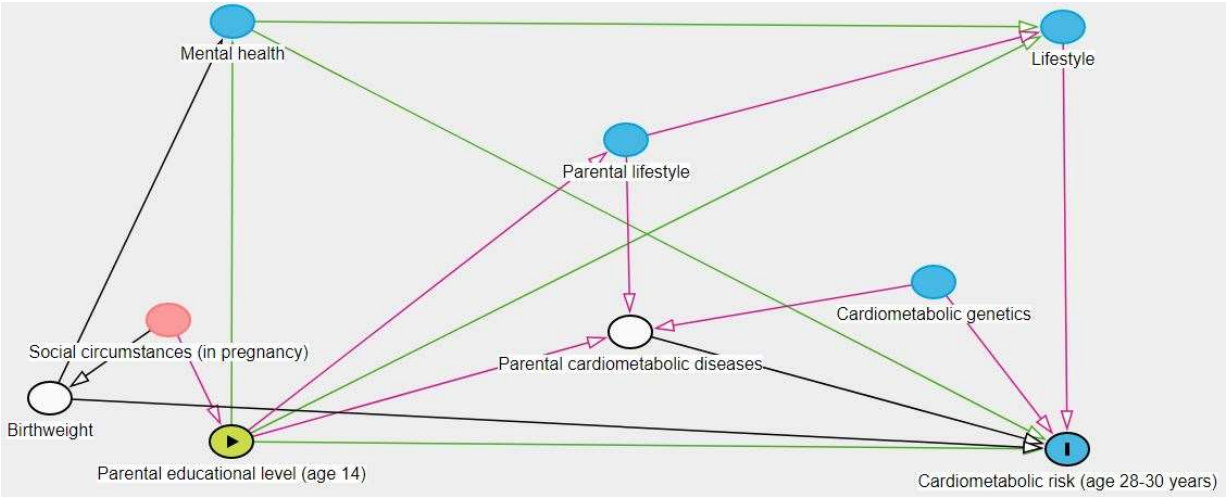
Various approaches can help eliminate the risk of confounding in observational studies. Statistical methods include stratification and adjustment. Furthermore, confounders can be controlled for in the study design by restricting the study population to specific subgroups.

The study population of the West Jutland Cohort is restricted to individuals born in 1989. Thus, age as a potential confounder was eliminated by design. In study 1, we stratified by sex and did not include any other confounders. In studies 2 and 4, we used the historical approach to define confounders based on previous knowledge and the literature. Study 3

was conducted within the causal inference framework, and we used a DAG to identify potential confounders. In a DAG, confounders are identified through the back door criterion assuming that the DAG sufficiently depicts the causal structures(138). One of the advantages of conducting the mediation analyses using nested counterfactuals is the ability to include exposure-mediator interaction and different confounder structures. The mediation analysis involves assumptions of no uncontrolled confounding in the relationship between: 1. exposure-outcome, 2. exposure-mediator, 3. mediator-outcome and 4. mediator-outcome induced by the exposure(137). Assumption number 2 may be violated by parental mental health. This is the case if parental mental health is a descendent of previous mental health which has affected parental educational attainment. Furthermore, parental mental health may affect the mental health of the offspring. Additional analyses using parental self-reported psychiatric disorders in 2004 as a proxy for mental health changed the proportion mediated to 13% and 16% using the educational level of the mother and father, respectively. This induces some assurance regarding the original findings. However, the results of the additional analyses should be considered with some caution due to a rather low response rate of 68% and 78% to this specific item in the parental questionnaires. Following the primary analyses in study 3, we also conducted additional analyses including physical activity and parental cardiometabolic disease history as confounders of the mediator-outcome and exposure-outcome associations. These adjustments reduced the proportion mediated by mental health in the association between childhood SEP and cardiometabolic disease risk considerably. However, including these variables as confounders violates the assumptions of the original DAG and removes the mediating impact from physical activity which we

assume causes an underestimation of the proportion mediated by mental health. Furthermore, including parental cardiometabolic disease history induces collider stratification bias of the estimates given that the DAG depicts the causal structures correctly (Figure 17).

Figure 17. Simplified DAG after adjustment for parental cardiometabolic disease history, study 3 (dagitty.net)



In summary, we included various approaches to deal with confounding in the studies presented in this dissertation. However, we cannot exclude that some confounding remains. This could be caused by misclassification of the observed confounders or unmeasured confounders that we were not aware of.

Statistical considerations

Statistical considerations have been touched upon throughout the dissertation. However, some additional comments are presented in the following. Overall, we displayed all data routinely to check for outliers, visible errors and distributions. When required, we did post-estimation plots for inspection. There could be a risk of chance findings (false

positive conclusions) due to multiple testing of risk markers in study 1. We conducted additional analyses and accounted for multiple testing by adding the Bonferroni correction. This did not change the main findings of the study. In study 2, we investigated four life course hypotheses simultaneously. In this study, we did not adjust for multiple hypotheses testing. Applying a correction would indeed reduce the risk of false positive conclusions. However, it is a more restrictive approach and would be a trade off with regard to the power of the study. This could potentially introduce false negative results(145). Consequently, since all of the life course models were pre-established hypotheses, we decided not to apply multiple hypotheses adjustment in the study. In study 3, we did a counterfactually based mediation analysis. The average total effect is defined as the hypothetical contrast had everyone been exposed versus had no one been exposed. As this information in its nature cannot be acquired, we had to rely on three core assumptions to justify the analyses: counterfactual consistency, conditional exchangeability and positivity(146-149). Counterfactual consistency requires that the potential outcome given the actual exposure is equal to the observed outcome. This assumption generally holds when the exposure is well defined. Conditional exchangeability is analog to no uncontrolled or residual confounding and no selection bias. This was discussed in the respective sections above. Positivity refers to the probability of being either exposed or unexposed, which has to be non-zero for every combination of exposures and confounders. These assumptions are not testable and we cannot exclude violations. Hence the results should be considered with some caution. In study 4, we used hierarchical linear regression models in order to provide the reader with transparency of the results. Unfortunately, we did not have questionnaire information

about SSS at ages 18 and 21, which would have been valuable based on the different findings at ages 15 and 28.

Generalizability

The source population of this dissertation is a well-defined complete regional cohort of individuals born in 1989. A prior study found the social structures of the region comparable to other parts of Denmark(150). Given a high internal validity (as discussed above in this chapter), the findings presented in this dissertation may be generalized to other comparable populations. However, of particular importance in relation to studies 2–4 is that Denmark is considered a welfare state with high degree of social security and a rather egalitarian society as measured by the Gini-coefficient(151). Transferring the findings from the studies in this dissertation directly to other settings may be difficult. Studies have found greater health differences across SEP strata in less egalitarian societies. Consequently, the Danish study context would most likely reduce the overall associations between SEP and health compared to societies with less established welfare policies and social security systems. Furthermore, the population of the West Jutland Cohort mainly consisted of Caucasians, and we were unable to conduct analyses within strata of race/ethnicity. Psychosocial and biological effects may vary across race/ethnicity, and it is uncertain whether these findings can be generalized to other populations. The CMR score used in studies 2–4 was a population-specific score and cannot be directly compared with other studies or generalized to other populations. However, since we evaluated associations rather than absolute values of the CMR score, the findings should be possible to relate to studies of comparable populations.

6

Chapter 6, Discussion of main findings in relation to existing literature

Study 1

The global burden of obesity in children and young adults highlights the importance of understanding the pathogenic associations between BMI and cardiometabolic disease risk in young age(13, 152). Furthermore, identification of young adults at high risk of cardiometabolic diseases is difficult. Most established risk assessment tools classify young adults as being at low risk merely based on their age(153, 154).

The CARDIA study, a prospective cohort study from four US locations (N = 5,115), found a prevalence of coronary artery calcification (CAC) in 10.2% of participants aged 32–46 years(155). The Muscatine Study, a representative sample of a cohort from the US state of Iowa (N = 383), found a prevalence of CAC in 31% of men and 10% of women aged 29–37 years, with increased risk among those with higher levels of BMI. The CAC Consortium, an ongoing multi-center study (N = 22,346), found a CAC prevalence of 21.8% in individuals aged 30-39 years with increased risk among those who were overweight and obese compared to those with normal weight(156, 157). This is in contrast to the very limited CAC prevalence in the current study. Despite a relatively young study population in the CARDIA study and the Muscatine Study, the participants were older than the participants in the current study. The members of the study population in the CAC Consortium were asymptomatic; however, they underwent CAC testing based on clinical indications such as hyperlipidemia or a family history of cardiovascular disease. The

inconsistent findings may be attributed to these differences across study populations. CAC evaluated by computed tomography is considered a reliable measure of plaque burden associated with later coronary events(158). However, it does not evaluate non-calcified plaques or increased intima-media thickness. Unfortunately, we were unable to evaluate the association between BMI and the carotid intima-media thickness that can precede the calcification of the coronary arteries and thus be a valuable marker of sub-clinical cardiometabolic disease risk in young adulthood(159).

In the current study, we did not include duration of obesity. Norris et al. conducted a pooled study using three British birth cohorts and found that a greater obesity duration was positively associated with multiple cardiometabolic risk markers(160). We do have information available about self-reported height and weight at ages 15, 18 and 21 in the West Jutland Cohort Study, and investigating trajectories of BMI in relation to cardiometabolic disease risk would be of interest. A systematic review and meta-analysis by Umer et al. evaluated longitudinal associations between childhood obesity and adult cardiovascular disease risk. They found minor and statistically insignificant associations between childhood obesity and total cholesterol and LDL-cholesterols(161). Furthermore, the study found that childhood obesity was statistically significantly and inversely associated with adult HDL-cholesterols and positively associated with adult triglycerides. These findings are consistent with the findings in the current study and give some reassurance as to the legitimacy of the findings despite the cross-sectional design. We found striking variations across strata of BMI in levels of interleukin-6, fibrinogen and hs-CRP. Markers of inflammation are consistently associated with cardiometabolic diseases(162). Worth mentioning is, however, that the clinical importance of the variance

in these risk markers in relation to cardiometabolic pathogenesis is unknown(162, 163). Small variances in traditional risk markers could account for a larger variance in later disease risk than large variances in markers of inflammation. This is an ongoing topic and remains for future research to clarify(164). Nevertheless, the differences across strata of BMI in young adulthood prior to coronary artery calcification are noteworthy.

Study 2

Our findings in study 2 add further support to the evidence of an inverse association between educational level of the mother and cardiometabolic disease risk in young adulthood. On the contrary, we found no association between household income, another indicator of childhood SEP, and cardiometabolic disease risk. The different findings may partly be due to the study context in a Danish welfare society, where psychosocial factors in childhood, represented by educational level of the mother, could be more important than material resources, represented by household income, in relation to future cardiometabolic health. On the other hand, a Danish study by Kriegbaum et al. found that the risk of incident acute myocardial infarction increased with lower levels of accumulated income across the adult life course(165). These findings highlight the importance of using different SEP indicators in various settings (study contexts and age groups) in order to identify the indicator reflecting the aspects of relevance(30). We found no period in childhood with a distinct association with later cardiometabolic disease risk, and no specific association between intergenerational social mobility and cardiometabolic disease risk. The latter might be due to the statistical method, DRM, used in the study. As opposed to more conventional regression

approaches, the DRM estimates the importance of intergenerational social mobility independent of the effects of the destination(136). Our findings are in line with the review by Pollitt et al. stating that the cumulative life course model is the best fitting model in relation to adult cardiovascular outcomes(22). However, the causal link between educational level across the life course and later disease risk needs further investigation. The pathway model might be helpful in this regard. Childhood circumstances related to educational level of the mother such as health literacy, social support, psychological distress and cognition may be important factors in relation to both adult educational attainment and cardiometabolic disease risk, explaining some of the relationship. Falkstedt et al. conducted a longitudinal study of 49,321 male conscripts in Sweden(166). They found that pre-adult social, cognitive and behavioral factors explained more of the association between childhood SEP and risk of coronary heart disease in middle age than adult SEP, indicated by occupational status and educational level. Likewise, a propensity matching analysis (N = 553) by Loucks et al. found that early life factors, such as childhood intelligence and parental SEP, explained some of the association between adult educational level and coronary heart disease risk evaluated by the Framingham risk algorithm(167). These are examples of how the different models can overlap and jointly point to the direction of future research and public health initiatives.

Study 3

Study 3 investigated the impact of accumulated mental health at ages 15–28 on the association between parental educational level and cardiometabolic disease risk in young adulthood. We quantified the proportion mediated by mental health to be 10% and 12%

evaluating the educational level of the mother and father, respectively. Few studies have investigated this empirically, and the findings so far show mixed results. Winning et al. found that accumulated psychological distress at ages 7–16 mediated 37% of the association between childhood social disadvantage and a composite CMR score at age 45 in the 1958 British Birth Cohort (N = 6,027). These results are similar to the findings of the current study. However, the magnitude of the proportion mediated is larger. The construct of the mediator and outcome measures are highly comparable in the two studies. However, the age periods evaluated are not entirely alike. Furthermore, the exposure measures vary because the study by Winning et al. uses a composite measure including family hardship, which may capture the association with childhood distress better than the single SEP indicator used in the current study. This could partly explain the different magnitude of the proportion mediated in the two studies. Lee et al. investigated latent classes derived from various measures of childhood SEP/stressful experiences and a composite CMR score at ages 24–32 in the ADD Health study (N = 9,421)(168). They found associations between low SEP/stressful experiences and increased CMR and an indirect effect through lifestyle and depressive symptoms in adolescence and young adulthood. The two mediators were evaluated simultaneously in the primary analyses and the proportion mediated was not quantified. Furthermore, the authors conducted a sequential mediation analysis and revealed that depressive symptoms were a descendent of low childhood SEP and preceded risky lifestyle. This overall pathway significantly predicted later increased CMR. Doom et al. also used the ADD Health study to investigate pathways between adolescent SEP, evaluated by a composite score, and a Framingham-based risk score(102). They found indirect pathways

through adult educational level and lifestyle but not through depressive symptoms. Some methodological considerations could explain the different findings. Firstly, as mentioned earlier, the findings could be confounded if both adult educational attainment and psychological factors have common ancestors. Secondly, the Framingham-based risk score included smoking, and it is, therefore not entirely comparable with the other studies. Thirdly, evaluating multiple mediators measured at the same time simultaneously might hinder strong inferences about causality(169). In conclusion, future studies evaluating the mediating impact of mental health are needed. These should preferably include larger study samples, multiple measures of mental health, a longitudinal design and appropriate statistical methods.

Study 4

Study 4 investigated the association between SSS at ages 15 and 28, and the CMR score at ages 28–30. Experimental studies and studies among non-human primates have to some extent confirmed the importance of status perception in relation to cardiometabolic disease risk. For example, experimentally manipulated low SSS decreased heart rate variability in a study by Pieritz et al., indicating autonomic imbalance(170). Furthermore, studies in monkeys found differences in CAC and autonomic and neuroendocrine functioning among the subordinates compared to the dominants(171).

Our literature review reveals that the current study was the first to evaluate this association prospectively using adolescent SSS. Prior studies, mostly cross-sectional, evaluated the association between SSS and various measures of cardiometabolic disease risk in adulthood. A meta-analysis by Tang et al. in 2016 evaluated nine studies and found

an inverse association between SSS and different cardiometabolic outcomes(172). The association attenuated after inclusion of objective measures of SEP, however, the trend remained. The findings regarding the evaluation of SSS at age 28 in the current study are thus in line with the majority of studies. In contrast, some studies find no association or positive associations. A study among black women aged 24–32 years (N = 581) in the United States found no association between SSS and blood pressure(173). Likewise, a study from Taiwan (N = 1,023) among individuals aged 54–91 years found no association between SSS and a measure of allostatic load(174). In addition, a study from low-income regions in Mexico (N = 9,362) among women aged 18–65 years found a reverse gradient with a positive association between SSS and blood pressure(175). These conflicting findings could however, be due to differences in study context, study population and age. Furthermore, there is some inconsistency regarding the sex differences observed between SSS and disease risk. Consistent with the findings from the current study, McClain et al. found stronger associations for women than for men in an investigation of SSS and various cardiometabolic risk markers (N = 5,114), while Freeman et al. found stronger associations for men evaluating SSS and hs-CRP (N = 13,236)(38, 176). This remains for future research to clarify, but sex differences could be explained by different conceptualization of the SSS measure as well as different pathophysiological responses to status inferiority(177-179).

As mentioned in the introduction, the relevance and predictive value of the measure is a topic of debate. Singh-Manoux et al. from the Whitehall II study propose that SSS involves "*the cognitive averaging of standard markers of socioeconomic position, while taking into account one's assessment of current and future prospects*"(37). This is further supported

by a study from Brazil showing that adult SSS was a complex measure of various individual and family SEP indicators across the life course(36). The findings of the current study support the notion of SSS being a unique measure providing complementary information in addition to objective measures of SEP.

7

Chapter 7, Main conclusions

Within the last 80 years, researchers and clinicians have struggled to understand the underlying pathologies and social determinants of cardiometabolic diseases. The evaluation of cardiometabolic disease risk early in life remains a topic of investigation.

Firstly, we conducted a cross-sectional examination of BMI and various cardiometabolic risk markers in young adults. We found that obesity was associated with increased insulin levels and low-grade inflammation prior to widespread impaired glucose homeostasis, increased traditional cardiovascular risk markers, and detectable calcium formation measured by cardiac computed tomography.

Secondly, we found an inverse association between childhood SEP, indicated by parental educational level but not household income, and cardiometabolic disease risk in young adulthood. We found no indication for a specific timing effect in childhood and no specific association with intergenerational social mobility. However, we found that accumulated low SEP was associated with increased cardiometabolic disease risk. Investigating the underlying mechanisms between childhood SEP and cardiometabolic disease risk empirically, we found that mental health, lifestyle and adult educational attainment potentially act as intermediates of the association.

Finally, the individual perception of status in the social hierarchy at age 28 was inversely associated with cardiometabolic disease risk. This association seemed stronger for women compared to men and was largely independent of lifestyle and objective measures of SEP. Perceived social status at age 15 did not have a strong lasting association with later cardiometabolic disease risk.

Overall, cardiometabolic disease risk in young adulthood increased with low childhood SEP and low perceived social status. Multiple modifiable intermediates are involved in this biological embedding of social circumstances. The life course is a sequence of transitions, and the findings in the studies in this dissertation highlight the need to recognize the underlying pathophysiological mechanisms as dynamic complexes with various potentials for modulation across different periods. The findings provide further insight into understanding the intertwined mechanisms of biological, behavioral, psychological and social factors in order to identify targets for intervention and prevention.

8

Chapter 8, Perspectives and future research

Definite knowledge about risk markers in young age is warranted to identify young individuals at high risk and to tailor effective preventive strategies for cardiometabolic diseases. The findings from study 1 hold promise that identification of high-risk young adults may be possible preceding coronary artery calcification. The specific role of inflammation in the pathogenesis of cardiometabolic diseases is yet undetermined and needs further investigation in young study populations. However, refined risk assessment including inflammatory markers could provide valuable insight. Screening young, asymptomatic individuals with computed tomography of the heart to identify risk markers cannot be supported by the findings of study 1 in this dissertation.

While increasing numbers of studies examine the association between childhood SEP and cardiometabolic disease risk, specific knowledge about the underlying mechanisms is incomplete. The responsibility of the research community includes uncovering and quantifying potential targets for intervention in the association between low childhood SEP and later disease risk. The findings in the studies in this dissertation point to perceived social status as a unique measure of social circumstances. If low status perception in itself increases the risk for cardiometabolic diseases, evaluation of interventions to reduce this effect is recommended. This includes upstream interventions to increase social participation and downstream interventions to reduce the psychosocial and behavioral consequences of low status perception. We further quantified the impact of mental health in the association between childhood SEP and cardiometabolic disease risk among a sub-group of young Danish adults. This should preferably be supplemented

with other longitudinal studies in larger population samples in different settings. If the findings can be replicated, this would support a causal relationship and direct potentials for intervention. Other knowledge gaps in the association include the impact of cognition, adverse childhood experiences, health literacy and social network. A very recent Danish register study finds that a high proportion (74%) of children from low SEP families (parental educational level <10 years) experience medium to severe adversity in childhood(180). Investigating the mediating impact of adverse childhood experiences on the association between childhood SEP and cardiometabolic disease risk in young adulthood would be of great interest. The West Jutland Cohort Study has the potential to combine register-based information about adversities with questionnaire information and clinical measurements. A greater effort to demonstrate how low childhood SEP translates into increased cardiometabolic disease risk would be the best way to target policies and public initiatives. We need to acknowledge measures of SEP as indicators of other conditions in life rather than independent risk factors. As the social gradient was reversed in some study contexts, it seems reasonable to assume that the cultural preferences regarding known risk factors, i.e. stressors and behavioral factors, among the different societal groups are important and modifiable.

Real-life perspectives

In the studies on which this dissertation is based, we found inverse associations between parental educational level, perceived social status, but not household income, and later cardiometabolic disease risk. The findings should be considered in the context of a Danish egalitarian, welfare society. Former conflicting theories of material versus psychosocial

explanations of health inequality might not be that conflicting. We argue for a different approach. Material circumstances involve not only individual-level material resources but also the cultural and societal structures involved. These include welfare policies, access to education, healthcare, healthy food, exercise and clean air. The negative findings concerning household income in the current study, as opposed to other study contexts, may potentially act as an indicator of how macro-level structures can influence individual-level health and remove some of the impact of childhood SEP. This however, needs further attention in future studies. Yet, redistribution of material resources does not seem sufficient to impede the association between a low parental education and increased cardiometabolic disease risk. In view of the complex and interrelated factors, it seems necessary to collaborate across various sectors in society in a multidisciplinary approach. In Denmark, children spend much time away from home. Strengthened public day care facilities and schools could facilitate children from a low SEP achieving their best regarding cognition and mental well-being(181). Access to sport facilities, leisure activities and healthy food may possibly potentiate health, social network and social participation across all SEP strata. Additionally, societal responsibility has to include considerate attention to the individual child and family including family functioning, parenting skills and adverse childhood experiences. Furthermore, the benefit of the advances in conventional cardiometabolic treatment and prevention has not been equally distributed across SEP, potentially leading to a relative increase in cardiometabolic disease risk inequality(182). Improved health literacy in addition to accessible public health communication may help decrease the social inequality in cardiometabolic diseases(183).

In summary, improved understanding of the underlying mechanisms of the inverse association between childhood SEP and later cardiometabolic disease risk is critical to inform policy makers and improve upstream cardiometabolic prevention strategies in various societal settings. Ultimately, we need to support sustainable and healthy trajectories for children growing up in low SEP environments rather than treating their diseases when they grow older.

Summary

Dansk resumé (Danish summary)

Baggrund:

Kardiometaboliske sygdomme er, globalt set, den primære årsag til tidlig sygelighed og død hos voksne. Årsagerne til disse sygdomme er multifaktorielle. Traditionelle risikofaktorer omfatter genetik, overvægt og usund livsstil. Derudover er der social ulighed i andelen, der rammes af disse sygdomme. Litteraturen peger på, at den sociale ulighed starter i barndommen, men de underliggende mekanismer er ikke endeligt afdækket.

Formål og metode:

I denne afhandling ønsker vi at undersøge, hvordan socioøkonomiske forhold i barn- og ungdom relaterer til kardiometabolisk risiko hos unge danske voksne. Ultimativt ønsker vi at afdække modificerbare risikofaktorer, der kan benyttes i et forebyggelsesmæssigt perspektiv for at mindske den sociale ulighed i kardiometaboliske sygdomme. For at undersøge dette empirisk kobler vi informationer fra nationale registre med fortløbende spørgeskemaer og en klinisk undersøgelse af en undergruppe (N=264, alder 28-30, 50 % kvinder) af en dansk ungdomskohorte.

Resultater:

Studie 1 er en tværsnits-undersøgelse. Vi undersøgte hjertets kranspulsårer ved brug af computertomografi og fandt ingen klinisk betydelige forkalkninger hos deltagerne. Vi undersøgte desuden forskellige kardiometaboliske risikomarkører på tværs af strata af body mass index. Vi fandt små forskelle i traditionelle risikomarkører, så som total

kolesterol. Derimod fandt vi markante forskelle når vi sammenlignede niveauerne af inflammatoriske markører, eksempelvis høj-sensitiv CRP, samt niveauer af insulin på tværs af body mass index.

I studie 2 og 3 fandt vi, at kort uddannelse hos forældre, men ikke lav husstandsindkomst, i barndommen relaterede til øget kardiometabolisk risiko i tidligt voksenliv. Vi fandt desuden, at psykiske faktorer, livsstil og egen uddannelse kunne være medvirkende faktorer i denne sammenhæng.

I studie 4 fandt vi, at lav subjektiv social status som 15- årig hos piger og som 28-årig hos begge køn, relaterede til øget kardiometabolisk risiko i tidligt voksenliv. Denne sammenhæng var i stor udstrækning uafhængig af livsstil samt objektive mål for socioøkonomiske forhold.

Perspektiver:

Denne afhandling er med til at belyse de indbyrdes forbundne biologiske, adfærdsmæssige, psykologiske og sociale forhold, der danner grundlag for den sociale ulighed i risikoen for kardiometaboliske sygdomme. Resultaterne understøtter en tværfaglig og holistisk tilgang i barn- og ungdom for at understøtte vedvarende sundhed hos alle børn, også de, der vokser op i familier med lavere socioøkonomiske forhold.

English abstract

Background:

Cardiometabolic diseases remain the leading causes of premature mortality and morbidity in adult populations worldwide. Cardiometabolic diseases are multifactorial. Traditional risk factors include genetic predisposition, age, overweight/obesity and unhealthy lifestyle. Furthermore, social inequality in the risk of cardiometabolic diseases is an increasing health issue. Mounting evidence suggests that the inequality is rooted in childhood. However, the exact mechanisms remain unexplained.

Objective and methods:

In the studies in this dissertation, we aimed to empirically examine the association between childhood socioeconomic position (SEP) and cardiometabolic disease risk in young Danish adults. The ultimate purpose was to gain insight into modifiable risk factors in order to outline future perspectives to decrease the social inequality in cardiometabolic diseases. We used a combination of national registers, longitudinal questionnaire data and clinical measurements from a subsample (N = 264, ages 28–30, 50% women) of a Danish youth cohort.

Findings:

In study 1, we investigated cross-sectional differences across strata of body mass index and multiple cardiometabolic risk markers. No clinically significant coronary artery calcifications were detected in any of the strata by computed tomography. We found minor or no differences in levels of traditional risk markers, e.g. total cholesterol across

strata of body mass index. In contrast, we found substantial differences in markers of inflammation and glucose metabolism, e.g. high-sensitive C-reactive protein and insulin across strata of body mass index.

In studies 2 and 3, we found inverse associations between parental educational level in childhood, but not household income and cardiometabolic disease risk in young adulthood. Our findings furthermore point toward mental health, lifestyle factors and adult educational attainment as intermediates of the association.

In study 4, we found inverse associations between subjective social status at age 15 for girls and age 28 for both sexes, and cardiometabolic disease risk in young adulthood. The associations were largely independent of lifestyle factors and objective measures of SEP.

Perspectives:

The findings in the studies in this dissertation provide further insight into the intertwined mechanisms of biological, behavioral, psychological and social factors in relation to social inequalities in cardiometabolic disease risk. The findings support a multidisciplinary and holistic approach in childhood and youth to support the continuing health of all children, including those growing up in families with a lower SEP.

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Appendices

Appendices

Appendix 1. Overview of search queries and outcome of the literature search January 2022

Domain	No.	Search terms	Hits PubMed	Hits PsycInfo	Hits Embase
Childhood SEP	1	"childhood"[tiab] OR "life course"[tiab] OR "lifecourse"[tiab] OR "lifespan"[tiab] OR "life span"[tiab] OR "early life"[tiab] OR "earlylife"[tiab]	357,472	102,588	446,568
	2	parent*[tiab] OR "mother*"[tiab] OR "father*"[tiab] OR "maternal"[tiab] OR "paternal"[tiab]	865,257	290,073	1,101,840
	3	"social class"[majr] OR "socioeconomic factors"[majr] OR "education"[majr] OR "income"[majr]	717,699	241,751	134,666
	4	(1 OR 2) AND 3	47,123	30,690	11,928
	5	"social mobility" [tiab]	965	1,093	809
Cardiometabolic disease risk	6	"cardiovascular diseases"[majr] OR "glucose metabolism disorders"[majr] OR "dyslipidemias"[majr] OR "allostasis"[majr] OR "cardiometabolic risk factors"[majr]	2,578,985	5,933	123,194
	7	(4 OR 5) AND 6	1,306	116	52
Exclusion	8	7 NOT ("covid 19"[MeSH Terms] OR "diabetes, gestational"[majr] OR "diabetes mellitus, type 1"[majr] OR "congenital abnormalities"[majr])	864	114	51
Final search	9	8 AND english[Filter]	828	114	49

Appendix 2. Schematic overview of literature investigating childhood socioeconomic position and adult cardiometabolic disease risk published January 2016 to January 2022

Author Journal Year	Study/cohort name Country Age (at time of outcome)	N	Exposure (SEP-indicators)	Outcome	Key findings	Additional comments
- Zhang et al(184) **- Scientific reports** **- 2021**	- CHARLS - China - Mid-late adulthood	15,132	- Parental education - Parental occupation - Family finances	Type 2 diabetes (T2D)	- Direct pathway from low childhood SEP to T2D - Indirect pathway through adulthood SEP, physical activity, childhood health and food storage	Self-reported exposure and outcome
- Suh et al(185) **- Scientific reports** **- 2021**	- KNHANES - Korea - 19-80 years	37,992	Parental education	Hypertension (HTN)	- Low childhood SEP predicts prevalent HTN in young adults (19-39 years) but only marginally or not in middle-aged and older adults - Association attenuates after adjustment with adult SEP	
- Lopes et al.(90) **- American Journal of Hypertension** **- 2021**	- ELSA-Brasil - Brazil - 35-74 years	8,754	- Childhood: Maternal education - Youth: Occupational class of household head - Adulthood: occupational class - Intergenerational social mobility	HTN	- Low SEP in childhood, youth and adulthood associated with HTN incidence - Cumulative low SEP at greatest risk - Downward and upward mobility with marginally higher incidence compared to high stable and lower incidence compared to low stable	3.5 years follow-up
- Huang et al.(186) **- Canadian Journal of Cardiology** **- 2021**	- Individuals born 1977-1996 - Denmark - 20-40 years	1,123,600	Maternal education	Early-onset cardiovascular disease (CVD)	Childhood low SEP and medium SEP increased the risk of early-onset CVD with 27 % and 12 %, respectively	- Register-based - Findings were independent of family history of CVD and sex
- Gugushvili et al.(89) **- PloS one** **- 2021**	- Add Health - United States - 25-32 years	4,713	Intergenerational social mobility derived from combined measures of parental and adult education and occupation score	Allostatic Load (AL) score	- SEP-gradient among social immobile - SEP origin and destination equally important - Upward mobility was associated with lower AL-score. - Downward mobility was not associated with AL-score	Data analyzed with diagonal reference models (DRM)
- Zaborenko et al.(187) **- The Gerontologist** **- 2020**	- HRS - United States - >50 years	12,473	Composite measure of parental education, family finances and paternal occupation	Incident stroke or death due to stroke	- Childhood inverse SEP-gradient in unadjusted models - No association after adjustment with adult SEP, diseases and health behavior	- Adolescent depressive symptoms were the main influent on stroke risk
- Yang et al.(188) **- Journals of Gerontology: Social Sciences** **- 2020**	- ADD Health, MIDUS and HRS - United States - 24-34 (ADD Health), 35-64 (MIDUS) and >65 years (HRS)	- 10,597 (ADD Health) - 735 (MIDUS) - 6,381 (HRS)	- Childhood: Parental education, household income, welfare receipt, subjective financial wellbeing - Adulthood: Education, household income and household assets	- CRP - Composite metabolic index (diastolic and systolic blood pressure, HbA1c, waist circumference, HDL-C, TC and triglycerides)	- Childhood inverse SEP-gradient in all age-strata for Metabolic function but waned with age for CRP - Adult education protective in all age-strata for CRP but waned with age for metabolic function - Adult wealth protective in middle-age and older age but not in young adulthood for both outcome measures	

- Robson et al.(189) **- Psychosomatic Medicine** **- 2020**	- 1946 NSHD - Great Britain - 60-64 years	1,059	- Childhood socioeconomic adversity score (maternal education, social class of the father, house facilities and clothes in childhood) - Childhood psychosocial adversity score (ACEs)	Four groups from dichotomized BMI (normal weight vs. overweight/obesity) and metabolic index (diastolic and systolic blood pressures, HbA1c, HDL-C, triglycerides and use of relevant medication)	- Socioeconomic adversity score more strongly associated with being metabolically unhealthy in individuals with overweight/obesity as compared to normal weight - Psychosocial adversity score was associated with being metabolically unhealthy in all strata of BMI	
- Nishida et al.(91) **- Ciência & Saúde Coletiva,** **- 2020**	- Brazilian EpiFloripa Cohort Study - Brazil - 20-63 years	1,720	- Childhood: Parental education - Adulthood: Education	HTN	- No association between childhood SEP and HTN - Cumulative high SEP had 34-37 % lower odds for HTN compared to cumulative low SEP - No significant impact of upward/downward mobility	SEP-mobility was analyzed with logistic regression models
- Najman et al.(190) **- International Journal of Public Health** **- 2020**	- MUSP - Australia - 30 years	1,297	Family poverty (income)	- HOMA-IR - TC/HDL-C ratio - HDL-C, diastolic and systolic blood pressure	- No statistically significant association between poverty and outcome measures for men - Increased cardiometabolic risk in women among those with family poverty	-Attrition greatest among those with greatest poverty - More women than men included - Point estimates similar for men and women
- Miller et al.(92) **- Journal of the American Heart Association** **- 2020**	- ADD Health and MIDUS - United States - 24-32 (ADD Health) and 25-78 years (MIDUS)	- 7,542 (ADD Health) - 1,877 (MIDUS)	- Social mobility derived from family income (ADD health) or combined parental education and welfare receipt (MIDUS) and adulthood household income (poverty)	Metabolic syndrome	- Life course inverse SEP-gradient in MIDUS but not in ADD Health - Upward mobile individuals had increased prevalence compared to consistently advantaged or disadvantages individuals in both samples - Downward mobile individuals and consistently disadvantaged participants had increased prevalence as compared to consistently advantaged participants	- Upward mobile individuals reported less psychological distress (perceived stress and depressive symptoms) compared to consistently disadvantages participants
- Mallinson et al.(191) **- Journal of epidemiology and community health** **- 2020**	- APCAPS and IMS - India - Mean age 37.5 years	14,011	Childhood and adulthood standard of living index (SLI) (household wealth)	Anthropometry, diastolic and systolic blood pressure, TC, HDL-C, triglycerides, glucose, insulin and HOMA-IR	- SLI inversely associated with blood pressure independent of adult SEP - No association between SLI and the other outcome measures	
- Glover et al.(93) **- American Journal of Hypertension**	- JHS - United States - 29-95 years	4,761	- Childhood: Maternal education - Adulthood: Education, income, occupation and wealth	HTN	- Higher childhood SEP associated with lower prevalence and incidence	The JHS is a cohort of African Americans

- 2020					- Upward mobility and consistent high SEP associated with higher prevalence but lower incidence compared to consistently low SEP	
- Präg and Richards(192) **- Journal of epidemiology and community health** **- 2019**	- Understanding society - Great Britain - >25 years	9,851	- Childhood: Parental occupational class - Adulthood: social class	AL-score	- Parental and adult SEP influence AL equally - No evidence for distinct effects of upward or downward mobility	- Data analyzed with DRM - AL-score did not include any original primary biomarker
- Martin et al.(193) **- Health Place** **- 2019**	- ADD Health - United States - 24-32 years	9,500	Neighborhood (in adolescence, emerging adulthood and young adulthood)	Metabolic syndrome	- Adolescent neighborhood directly associated with metabolic syndrome in young adulthood - No indirect association through neighborhood in adulthood	Authors conclude support for the latent effects but not the pathway life course model
- Lee et al.(168) **- Journal of Behavioral Medicine** **- 2019**	- ADD Health - United States - 24-32 years	9,421	Latent classes derived from community adversity, family economic hardship, parental education, single parent family and stressful experiences	CMR score created from ten biomarkers (systolic and diastolic blood pressure, pulse rate, HbA1c, glucose, triglycerides, HDL-C, LDL-C, hs-CRP and BMI)	- Direct effect from low SEP and stressful experiences to increased CMR risk - Indirect effect through lifestyle and depressive symptoms in adolescence and young adulthood	Authors conclude a multiplicative effect of adversity related to SEP and stressful experiences on CMR risk
- Juonala et al.(95) **- The Medical Journal of Australia** **- 2019**	- ABC study - Australia - 23-28 years	423	Specific area-level SEP index at birth (employment, income, housing and education)	BMI, systolic blood pressure, LDL-C, HDL-C, triglycerides	- Low SEP associated with lower BMI, blood pressure, LDL-C and HDL-C levels	Study population consisted of children born to Indigenous Australian mothers
- Huang et al.(194) **- Epidemiology** **- 2019**	- ADD Health - United States - 24-34 years	7,218	Maternal education	Metabolic syndrome	- Inverse association between SEP and risk of metabolic syndrome - Stronger associations for women than men	Results remained after accounting for life course mediators (maltreatment, lifestyle, adolescent BMI and adult education)
- Hossin, Koupil and Falkstedt(195) **- BMJ Open** **- 2019**	- The Stockholm Public Health Cohort - Sweden - 40-84 years	19,720	Parental occupation	CVD mortality	- Increased risk among those with manual versus non-manual parental occupation - The proportion mediated by adult education, adult occupation, lifestyle and BMI was 44 % of the total effect	- Participants aged 18-40 excluded due to rare outcome (n=2)
- Ejlskov et al.(196) **- The European Journal of Public Health** **- 2019**	- Individuals born 1961-1971 - Denmark - 30-54 years	793,674	Parental and adult income, occupation, education and a composite SEP-measure	CVD or diabetes	- Childhood inverse SEP-gradient for all indicators and CVD and diabetes - 29-55 % was mediated through adult SEP dependent on SEP-indicator and outcome - No sex-differences	-Counterfactual based analyses - Authors conclude that the findings support the pathway life course model

Danquah et al.(197) **- Scientific reports** **- 2019**	- RODAM - Ghana - 25-70 years	5,575	Parental education	Waist circumference and T2D	- Low childhood SEP associated with increased waist circumference in both sexes and T2D in women	Some of the association was explained by adult education and occupation
- Coelho et al.(198) **- Annals of Epidemiology** **- 2019**	- ELSA-Brasil - Brazil - 34-75 years	13,365	Maternal education	Arterial stiffness (carotid femoral pulse wave velocity)	- Inverse association between childhood SEP and arterial stiffness - Association was no longer significant when adjusting for adult education in Whites but remained in Browns and Blacks	
- Carrillo-Vega et al(199) **- BMC Public Health** **- 2019**	- MHAS - Mexico - >50 years	8,848	Childhood poverty ("no shoes during childhood" and "went to bed hungry")	Diabetes incidence and prevalence	- "No shoes in childhood" associated with increased disease risk - No association between "went to bed hungry" and disease risk	Aged <50 years excluded
- Bonaccio et al.(200) **- Epidemiology and community health** **- 2019**	- Moli-sani - Italy - ≥35 years	22,194	Trajectories of childhood house facilities, adult education and adult material resources	CVD death	- No independent association with low childhood SEP - Low cumulative SEP is associated with increased risk	- Median follow-up 8.3 years - Inflammatory markers marginally accounted for the association
- Beckles, Saydah and Loustalot(201) **- Ethnicity and Disease** **- 2019**	- JHS - United States - 33-92 years	4,023	Childhood: Parental education Young adulthood: Education Mature adulthood: Occupational class	T2D incidence	- Among women but not men low childhood SEP was associated with increased T2D risk - No association after accounting for adult SEP and lifestyle - Among women but not men upward SEP was associated with increased T2D risk compared to stable high SEP	- Follow-up 7.9 years - Study population consisted of non-diabetic African Americans at baseline - Life course AL did not explain association
- Sjöholm et al.(94) **- International Journal of Cardiology** **- 2018**	- ABC study - Australia - 23-28 years	686	Specific area-level SEP index at birth (employment, income, housing and education)	Ideal cardiovascular health (blood pressure, HbA1c, TC, BMI, physical activity, smoking and diet)	Ideal cardiovascular health was rare. However, lower SEP was associated with ideal blood pressure and ideal physical activity	Study population consisted of children born to Indigenous Australian mothers
- Ogunsina, Dibaba and Akinyemiju(96) **- Journal of global health** **- 2018**	- SAGE - China, Mexico, India, South Africa and Russia - >18 years	38,297	Life course SEP based on maternal and adult education	Blood pressure, BMI, diabetes and HTN (self-reported)	- Higher life course SEP was associated with increased risk of diabetes and HTN among men but not women - Higher life course SEP was associated with increased risk of overweight/obesity for both sexes	Some of the association might be explained by different access to health care and therefor non-differential information on outcome
- Kivimäki et al.(202) **- Lancet Public Health** **- 2018**	- The Young Finns Study - Finland - 22-48 years	3,002	- Childhood neighborhood - Cumulative life course neighborhood	-Systolic blood pressure, HDL-C,	- Low childhood SEP associated with increased HOMA-IR, insulin and glucose levels compared to high SEP	

				triglycerides, glucose, insulin, and HOMA-IR - Obesity, waist circumference, fatty liver, diabetes, HTN, carotid plaque and left ventricle mass index	- Cumulative low SEP associated with obesity, fatty liver, HTN and diabetes compared to high cumulative SEP	
- Christensen et al.(203) **- BMC Public Health** **- 2018**	- Copenhagen Perinatal Cohort - Denmark - Midlife (mean age 50 years)	361	Composite parental SEP score (occupation, education, type of income and accommodation)	AL	- Parental SEP was inversely associated with AL - Indirect effect through adult education but not intelligence, social relations or personality in young adulthood	
- Savitsky et al. **- (204)Journal of Epidemiology and Community Health** **- 2017**	- The Jerusalem Perinatal Family Follow-Up Study - Jerusalem - 32 years	1,132	Parental and adult occupation and education	Anthropometry, systolic and diastolic blood pressures, Glucose, insulin, HOMA-IR, LDL-C, HDL-C and triglycerides	- Low SEP in childhood and adulthood was associated with risk after mutual adjustments - Associations remained after adjusting for smoking and physical activity - Adverse outcome among downward and upward mobile individuals	Social mobility was investigated by linear regression models
- Savelieva et al.(205) **- Health Psychology** **- 2017**	- The Cardiovascular Risk in Young Finns study - Finland - 30-49 years	697	Childhood and adulthood composite scores (education, occupational status, income and occupational stability)	Ideal cardiovascular health (blood pressure, glucose, TC, BMI, physical activity, smoking and diet)	- Higher childhood SEP was associated with higher ideal cardiovascular health - Adult SEP accounted for 33 % of the association - Upward mobile individuals had better health as compared to stable low individuals	
- Puolakka et al.(206) **- Hypertension** **- 2017**	- The Cardiovascular Risk in Young Finns study - Finland - 24-45 years	2,566	Household income	Arterial stiffness (pulse wave velocity and carotid artery distensibility)	- Higher childhood SEP was associated with lower arterial stiffness - Association remained significant after adjustment for adult SEP	
- Laitinen et al.(207) **- JAMA Pediatrics** **- 2017**	- The Cardiovascular Risk in Young Finns study - Finland - 34-49 years	1,871	Household income	Left ventricular mass and diastolic performance	- Low childhood SEP was associated with increased left ventricular mass after accounting for traditional risk factors and adult SEP	
- Kilpi et al.(208) **- Social Science and Medicine** **- 2017**	- Sample of census in 1950 - Finland - 37-74 years	94,501	Parental education, occupation, household crowding and home ownership	Myocardial infarction incidence and mortality	- Childhood SEP associated with myocardial infarction. Stronger association for incidence than mortality - Adult education and income mediated the association	Various sex-differences observed concerning the different SEP-indicators

- Hostinar et al.(209) **- Psychosomatic Medicine** **- 2017**	- Vancouver, British Columbia - Canada - 15-55 years	354	Occupational status	Metabolic syndrome	- Inverse association between occupational status and metabolic syndrome risk - Adult SEP non-significantly associated with metabolic syndrome risk	
- Doom et al.(102) **- Social Science and Medicine** **- 2017**	- ADD Health - United States - 24-34 years	14,493	- Composite parental SEP (household income, neighborhood poverty and education)	Framingham-based CVD risk score (age, sex, BMI, smoking, systolic blood pressure, diabetes and antihypertensive medications)	- Inverse association between SEP and risk – Association remained significant after inclusion of all co-variates and mediators - Indirect path through lifestyle, financial stress, adult SEP and lack of health care - No indirect path through depressive symptoms, sleep problems or maternal support	Mediation through various pathways evaluated by path analysis
- Derks et al.(210) **- International Journal for Equity in Health** **- 2017**	- The Maastricht Study - The Netherlands - 40-75 years	3,263	Poverty and parental educational level	Pre-diabetes and T2D	- Inverse association between childhood SEP and risk of both outcome measures - Associations were independent of adult SEP	BMI partly mediated the association
- de Souse et al. **- International Journal of Public Health** **- 2017**	- ELSA-Brasil - Brazil - 35-74 years	13,544	Childhood: Maternal education Youth: Social class Adulthood: Education	Framingham Risk Score	- Inverse association between childhood SEP and CVD risk after accounting for adult SEP - Cumulative low SEP associated with increased risk - Upward, downward or stable low SEP had higher risk compared to stable high SEP	
- Winning et al.(211) **- Psychosomatic Medicine** **- 2016**	- 1958 British Birth Cohort - Great Britain - 45 years	6,027	- Composite score related to family (e.g. neglect and family illness) and socioeconomic hardship (overcrowding, unemployment, low parental occupational class, financial difficulties and housing difficulties)	CMR score (z-standardized CRP, fibrinogen, HDL-C, TC, triglycerides, HbA1c, heart rate, systolic and diastolic blood pressures)	- Social disadvantage associated with increased CMR - 37 % mediated through psychological distress in childhood and youth	Cumulative psychological distress score created from measures at ages 7, 11 and 16
- Walsemann, Goosby and Farr(41) **- Social Science and Medicine** **- 2016**	- ADD Health - United States - 24- 34 years	11,397	- Adolescent and adult SEP: composite z-standardized measures (income, education and occupation	Composite measure of waist circumference, blood pressure, HbA1c and CRP	- Support for all four life course models in varying degree across race/ethnicity and sex - Upward mobility associated with higher risk among white men as compared to stable high SEP - The pathway model significant among Latino women - No life course model significant for black men or women or Latino men	- Explicitly investigates all four life course models - Use regression analysis to investigate all life course models
- Turner, Thomas and Brown(212)	- Community sample, southern County - United states	1,252	- Childhood and adulthood composite standardized measure (education, occupation and family finances)	AL	- Inverse association between childhood SEP and AL - Statistically significant association remained after adjusting for adult stress and SEP	The study also examined self-rated health and doctor diagnosed illness.

- Social Science and Medicine **- 2016**	- 25-65 years					The inverse association with these outcome measures were explained by adult circumstances.
- Stringhini et al.(213) **- Scientific Reports** **- 2016**	- ELSA - England - ≥50 years	6,218	- Paternal occupation and education - Adult household wealth and a composite life course measure of the three above	T2D	- Inverse association between all SEP-indicators and risk - Inflammatory markers explained up to one third of the association - Lifestyle factors explained up to two thirds of the association	Lifestyle, CRP and fibrinogen were examined as mediators
- Puolakka et al.(214) **- Diabetes Care** **- 2016**	- The Cardiovascular Risk in Young Finns study - Finland - 34-49 years	2,250	Family income	- Metabolic syndrome - T2D and impaired fasting glucose	- Inverse association between childhood SEP and all outcome measures - Association remained after accounting for adult SEP and childhood risk factors concerning metabolic syndrome but became non-significant concerning T2D and glucose	Childhood risk factors included lipids, blood pressure, insulin, BMI, physical activity and diet
- Palm et al.(215) **- Atherosclerosis** **- 2016**	- The GENESIS study - Germany - 18-80 years	1,279	Composite score childhood, adolescence and adulthood (occupation, living conditions and family income)	Ischemic stroke	- Inverse association between childhood SEP and risk - Association was not explained by infectious burden, lifestyle factors and later SEP - Association became non-significant after adjustment with dental care factors	Case-control study
- Montez et al.(216) **- Journals of Gerontology: Social Sciences** **- 2016**	- SWAN - United States - 42-69 years	1,077	- Three latent classes derived from parental education, family ownership of car/house, difficulties paying for food or rent - Adulthood educational level	Metabolic syndrome prevalence and incidence	- Low childhood SEP marginally increased prevalent risk at baseline - Low adult SEP significantly increased prevalent risk at baseline - Partly mediated through lifestyle factors - Adult SEP but not childhood SEP was associated with incident risk during follow-up	- Study-population consisted of women only - Follow-up 17 years - Adult reproductive, economic, lifestyle and psychological factors were examined as mediators
- Liu et al.(217) **- Pediatrics** **-2016**	- The Cardiovascular Risk in Young Finns study - Finland - 30-45 years	1,015	Family income	Anthropometry, blood pressure, HDL-C, LDL-C, hsCRP, CIMT, carotid distensibility, brachial flow-mediated dilatation	- Inverse association between family income and outcome measures in various degree - Childhood infection-related hospitalizations significantly predict increased BMI, waist circumference and reduced brachial flow mediated dilatation in those from low SEP but not high SEP	Childhood infection-related hospitalizations (at age 0-5) was investigated
- Deere et al.(218) **- Ethnicity and Disease** **- 2016**	- JHS - United States - 33-92 years	4,756	Childhood: Material resources and maternal education Adulthood: Education and income	Prevalent left ventricular hypertrophy, peripheral artery disease, CAC and CIMT	- Positive association between childhood material resources and CIMT but no association regarding the other outcome measures - Inverse associations between adult SEP and all outcome measures apart from CAC	Analyses were adjusted with age, lifestyle and traditional CVD risk markers

- Cirera et al.(219) **- The European Journal of Public Health** **- 2016**	- EPIC-Spain Cohort - Spain - 40-70 years	36,296	Combined measure derived from paternal occupation and adult education	T2D incidence	- Inverse association between life course SEP and risk - Association was mediated through anthropometry but remained significant after this adjustment	Mean follow up 12.1 year
- Camelo et al.(220) **- Annals of epidemiology** **- 2016**	- ELSA-Brasil - Brazil - 35-74 years	12,960	- Cumulative life course model: education-based score and occupation-based score - Intergenerational social mobility	Diabetes incidence	- Inverse association between accumulated SEP and risk. More pronounced among men than women - Downward mobile individuals had higher risk compared to upward mobile and high-mobile individuals - Associations were non-significant for women but remained for men after adjustment with risk factors	Risk factors included lifestyle, blood pressure, anthropometry, HDL-C and triglycerides
- Barboza et al.(103) **- Social Science and Medicine** **- 2016**	- 1958 British Birth Cohort - Great Britain - 44 years	7,573	Maternal education and paternal occupation	AL	- Inverse associations between both SEP-indicators and risk - Associations were mainly mediated by educational, financial and lifestyle factors for both sexes - 45-60 % remained unexplained by the mediators	Financial, psychosocial, educational and lifestyle factors (including BMI) at ages 7-23 years was examined as mediators

Abbreviations: T2D, Type 2 diabetes; HTN, Hypertension; KNHANES, the Korea National Health and Nutrition Examination Survey; ELSA-Brasil, The Brazilian Longitudinal Study of Adult Health; HRS, Health and Retirement Study; CVD, Cardiovascular disease; AL, Allostatic Load; DRM, Diagonal reference models; ADD Health, Adolescent to Adult Health; MIDUS, National Survey of the Midlife Development in the United States; NSHD, National Survey of Health and Development; ACEs, Adverse childhood experiences; HDL-C, High density lipoprotein cholesterol; TC, total cholesterol; HbA1c, glycosylated hemoglobin; BMI, body mass index; MUSP, Mater-University of Queensland Study of Pregnancy; HOMA-IR; homeostatic assessment model of insulin resistance; APCAPS, Andhra Pradesh Children and Parents' Study; IMS, Indian Migration Study; SLI, Standard of living index; JHS, The Jackson Heart Study; CMR, cardiometabolic risk; hs-CRP, high sensitive C-reactive protein; ABC, Aboriginal Birth Cohort; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; RODAM, Research on Obesity and Diabetes among African Migrants; MHAS, Mexican Health and Aging Study; SAGE, Study on Global Ageing and Adult Health; ELSA, the English Longitudinal Study of Ageing; SWAN, the Study of Women's Health Across the Nation; CIMT, Carotid Intima-Media thickness; CAC, Coronary artery calcification

Appendix 3. Schematic overview of literature investigating subjective social status and adult cardiometabolic disease risk

Author Journal Year	Study name Country Age	Study design	N	Exposure of relevance	Outcome of relevance	Key findings of relevance	Additional comments
- Yong, Hartanto and Tan(221) **- Health Psychology** **- 2021**	- MIDUS and MIDJA - United States and Japan - 25-79 years	Cross-sectional	1,435	SSS (continuous)	CRP	- Inverse association between SSS and CRP for Americans - No association for Japanese	Further explores the moderating effects of anger and culture
- Piedra et al(222) **- Journal of the American Heart Association** **- 2021**	- HSCL/SOL - United States - 18-74 years	Cross-sectional	15,374	SSS (divided into tertiles)	Cardiovascular Health Index (diet, smoking status, physical activity, body mass index, cholesterol, blood pressure and fasting glucose)	Positive association between SSS and overall cardiovascular health	Study population consisted of Hispanic/Latino individuals
- McClain, Gallo and Mattei(38) **- Annals of Behavioral Medicine** **- 2021**	- ADD Health - United States - 24-32 years	Cross-sectional	5,114	SSS (divided into three categories based on the median score)	Waist circumference, BMI, blood pressure, HDL-C, LDL-C, triglycerides, hs-CRP, HbA1c, and glucose	- Overall inverse association between SSS and outcome measures - Race/ethnicity and sex differences in the associations - Differences across race/ethnicity in correlates between SEP and SSS	Further explores the moderating effects of race/ethnicity and sex
- Scott, Silva and Simmons(173) **- Health Equity** **- 2020**	- ADD Health (sub-sample) - United States - 24-32 years	Cross-sectional	581	SSS (dichotomized at the median score)	Blood pressure	No association between SSS and blood pressure	- Study population consisted of black females - Further examines sleep characteristics and adverse social exposures in relation to blood pressure
- Scholaske et al.(223) **- Brain Behavior Immunology** **- 2020**	- Health and disease research program - United States - Fertile women (no age available)	Longitudinal	250	SSS (continuous)	Composite inflammatory score in early, mid and late pregnancy (IL-6, CRP and TNF-alpha)	- Inverse association between SSS and outcome - No association between SEP and outcome	Study population consisted of pregnant women
- Cardel et al.(224) **- Psychoneuroendocrinology** **- 2020**	- JHS - United States - 35-84 years	Longitudinal	1,724	SSS (continuous)	Metabolic Syndrome score (z-derived)	- Inverse association between SSS and metabolic syndrome score	Study population consisted of African American

						- Significant interaction with sex (stronger association among women compared to men)	
- Harbison, Pössel and Roane(225) **- International Journal of Behavioral Medicine** **- 2019**	- Not available - United States - 18-62 years	Cross-sectional	240	SSS (continuous)	Diastolic and systolic blood pressure	Insignificant association between SSS and blood pressure	-Study population consisted of college students - Further examined the interacting effect with brooding (rumination)
- Demakakos et al.(226) **- European Journal of Epidemiology** **- 2018**	- ELSA - Great Britain ≥ 50 years	Longitudinal	9,972	SSS (continuous)	Cardiovascular mortality	- Inverse association between SSS and outcome - Stronger association among those aged 50-64 compared to those ≥ 65 years	- Unhealthy behaviors explained some of the association
- Freeman et al.(176) **- Psychosomatic Medicine** **- 2016**	- ADD Health - United States - 24-32 years	Cross-sectional	13,236	SSS (continuous)	Hs-CRP	- Inverse association between SSS and CRP - Association stronger among men compared to women	
- Gersten, Timiras and Boyce(174) **- Journal of Biosocial Science** **- 2015**	- SEBAS - Taiwan - 54-91 years	Cross-sectional	1,023	SSS (continuous)	Neuroendocrine allostatic load index and individual biomarkers (cortisol, DHEAS, adrenaline, noradrenaline and dopamine)	- No association between index and SSS - Some connection between DHEAS and SSS but no other outcome measures	
- John-Henderson(227) **- Annals of Behavioral Medicine** **- 2013**	- Not available - United States - 18-33 years	Cross-sectional	209	SSS (dichotomous / continuous)	IL-6	- Inverse association between SSS and IL-6	- Study population consisted of undergraduate students - Further explores moderating effects of implicit beliefs about social class
- Subramanyam et al.(228) **- Social Science and Medicine** **- 2012**	- JHS - United States - 21-95 years	Cross-sectional	5,301	SSS (continuous, z-transformed)	Waist circumference, HOMA-IR and diabetes	Inverse association between SSS and HOMA-IR among women but not men	- Study population consisted of African Americans - Further examined the moderating effect of perceived discrimination
- Demakakos, Marmot and Steptoe(229) **- European Journal of Epidemiology** **- 2012**	- ELSA - Great Britain ≥ 50 years	Longitudinal	7,432	SSS (continuous)	Incident diabetes	Inverse association between SSS and incident diabetes	-5.3 years follow-up
- Saxton et al.(230) **- Brain Behavior Immunology** **- 2011**	- Not available - United States - 18-33 years	Cross-sectional	112	SSS (continuous)	IL-6	- Inverse association between SSS and IL-6 - Early social experiences moderated the effect	- Study population consisted of undergraduate students

						- Differences across ethnicity	- Also did studies in laboratory rats
- Kowall et al.(231) **- Journal of Epidemiology and community health** **- 2011**	- KORA S4/F4 - Germany - 55-74 years	Longitudinal	887	Perceived social class (divided into three categories)	Incident diabetes or pre-diabetes	Low SSS had higher risk as compared to high SSS	- 7 years follow-up - No association between objective SEP and outcome
- Manuck et al.(232) **- Psychosomatic Medicine** **- 2010**	- AHAB - United states - 30-54 years	Cross-sectional	981	SSS (continuous)	Metabolic syndrome and its individual components	Inverse association between SSS and outcome	Including lifestyle in analyses did not change the findings
- Cooper et al.(233) **- Annals of Behavioral Medicine** **- 2010**	- Stress, blood pressure and ethnicity - United states - 19-53 years	Cross-sectional	72	SSS (continuous)	Flow-mediated dilation (endothelial dysfunction)	SSS-community (but not SSS-USA) was positively associated with flow-mediated dilation (indicating good endothelial function)	
- Fernald and Adler(175) **- Journal of Epidemiology and community Health** **- 2008**	- National Social Welfare survey - Mexico - 18-65 years	Cross-sectional	9,362	SSS (divided into tertiles)	Blood pressure	Positive association between SSS and blood pressure	- Study conducted in low-income regions - Study population consisted of women only
- Demakakos et al.(40) **- Social Science and Medicine** **- 2008**	- ELSA - Great Britain - ≥52 years	Cross-sectional	7,433	SSS (continuous)	Hypertension, diabetes, central obesity, HDL-C, triglycerides, fibrinogen and CRP	Inverse association between SSS and outcome in both sexes	- Further analyses suggested that SSS mediated the association between education (but not wealth) and some outcome measures
- Adler et al.(234) **- Social Science and Medicine** **- 2008**	- Whitehall II and CARDIA - Great Britain and Unites states - 47-67 (Whitehall II) and 33-48 (CARDIA) years	Cross-sectional	6,981 (Whitehall II) 3,632 (CARDIA)	SSS (Divided into five categories)	Hypertension	- Inverse association between SSS and hypertension except among black males in the CARDIA study - Stronger association among Whites in CARDIA compared to Whitehall II participants and Blacks in CARDIA	Comparison of two study populations
- Ghaed and Gallo(235) **- Health Psychology** **- 2007**	- Not available - United states - Mean age 41 years (SD=9.5)	Cross-sectional	92	SSS (continuous)	Blood pressure and BMI	- No association with BMI - SSS-community was inversely associated with blood pressure - SSS-USA was positively associated with blood pressure	Study population consisted of women only

- MacLeod et al.(236) **- Social Science and Medicine** **- 2005**	- Not available - Scotland - 35- 64 years	Longitudinal	5,232	Three categories of perceived work place status	Cardiovascular death or diseases	No significant associations	Study population consisted of men only
- Singh-Manoux et al.(37) **- Social Science and Medicine** **- 2003**	- Whitehall II - Great Britain - 35-55 years	Cross-sectional	6,981	SSS (five categories)	Angina and diabetes	- Inverse association between SSS and both outcome measures. - Stronger association for men compared to women	
Abbreviations: SSS, Subjective Social Status; MIDUS, The Midlife in the United States; MIDJA, The Midlife in Japan; CRP, C-reactive-protein; HSCL/SOL, Hispanic Community Health Study/Study of Latinos; ADD Health, National Longitudinal Study of Adolescent to Adult Health; SEP, Socioeconomic position (objective measure); SEBAS, Social Environment and Biomarkers of Aging Study, AHAB, Adult Health and Behavior; BMI, Body mass index; IL-6, Interleukin-6, HDL-C, High density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; HOMA-IR; homeostatic assessment model of insulin resistance; JHS, The Jackson Heart Study							
Search query: ("subjective social status"[Text Word]) OR ("macarthur scale"[Text Word]) OR ("perceived social status"[Text Word]) AND ("cardiovasc*"[Text Word] OR "cardio vascular"[Text Word] OR "cvd"[Text Word] OR "heart disease"[Text Word] OR "cardiometabolic"[Text Word] OR "cardio metabolic"[Text Word] OR coronar*[Text Word] OR "stroke"[Text Word] OR cerebrovasc*[Text Word] OR "myocardial infarction"[Text Word] OR arteriosclero*[Text Word] OR atherosclero*[Text Word] OR atheriosclero*[Text Word] OR "cimt"[Text Word] OR "carotid intima media"[Text Word] OR "blood pressure"[Text Word] OR hypertens*[Text Word] OR "diabetes"[Text Word] OR "pre diabetes"[Text Word] OR "homa"[Text Word] OR "fasting glucose"[Text Word] OR "insulin"[Text Word] OR cholesterol*[Text Word] OR "lipid profile"[Text Word] OR triglyceride*[Text Word] OR dyslipid*[Text Word] OR hyperchol*[Text Word] OR inflammat*[Text Word] OR "metabolic syndrome"[Text Word] OR "allostatic load"[Text Word])							

Appendix 4. Questionnaire items from 2004 included in the dissertation

Variable	Items
Physical activity	"How many hours a week during leisure time do you usually exercise or play sports where you are out of breath or sweating?” a) None b) ½ hour c) 1 hour d) 2–3 hours e) 4–6 hours f) 7 hours or more
Smoking	"Do you smoke?" a) No, never b) No (but I used to) c) Yes (not every week) d) Yes (Not every day but every week) e) Yes (every day)
Depressive symptoms	"During the past week, how much have you had the following feelings" (response categories: "not at all", "a little", "some" and "a lot") a) "I was happy this week" b) "I felt like kids I knew were not friendly or that they didn't want to be with me" c) "I felt sad" d) "It was hard to get started doing things this week"

Sense of coherence	1. How do you feel about the things you do every day? (response categories: "very interesting", "interesting", "OK", "boring" and "very boring") 2. About your daily life: (response categories: "very often", "often", "sometimes, "almost never" and "never") a) "How often do you do things that you think are meaningful?" b) "How often do you have the feeling that you don't really care about what goes on around you?" c) "How often do you have the feeling that there is little meaning in the things you do?"
Perceived stress	"In the last month, how often...?" (response categories: "very often", "fairly often", "sometimes", "almost never" and "never") a) "have you felt that you were unable to control the important things in your life" b) "have you felt confident about your ability to handle your personal problems" c) "have you felt that things were going your way?" d) "have you felt difficulties were piling up so high that you could not overcome them"
Self-esteem	"How much do you agree or disagree with the following statements? There are no right or wrong answers" (response categories: "strongly agree", "agree", "disagree", and "strongly disagree") a) "I feel that I have a number of good qualities" b) "I feel that I'm a person of worth at least equal to others" c) "I am able to do things as well as most other people" d) "I take a positive attitude toward myself" e) "On the whole, I am satisfied with myself" f) "All in all, I'm inclined to feel that I'm a failure"

Subjective social status	"Think of this ladder as representing where people stand in the Danish society. • At the top of the ladder are the people who are the best off- those who have the most money, the most education, and the most respected jobs. • At the bottom are the people who are the worst off- those who have the least money, least education, and the least respected jobs or no job. Think of your own family. Mark your response on the ladder below that best represents where you think your family stand in relation to other families in Denmark."  

Appendix 5. ICD-10 codes used to obtain information from the Danish National Patient register about parental cardiometabolic disease history

DE10*, DE11*, DE13*, DE14*, DE78*, DI10*, DI15*, DI20*, DI21*, DI25*, DI26*, DI27*, DI28*, DI34*, DI35*, DI36*, DI37*, DI42*, DI46*, DI51*, DI60*, DI61*, DI62*, DI 63*, DI64* DI65*, DI66*, DI67* DI70*, DI71*, DI72*, DI74*, DR030, DR73*, DZ863D

Appendix 6. Correlations (Spearman's rho) between cardiometabolic risk markers and body mass index for each sex, study 1

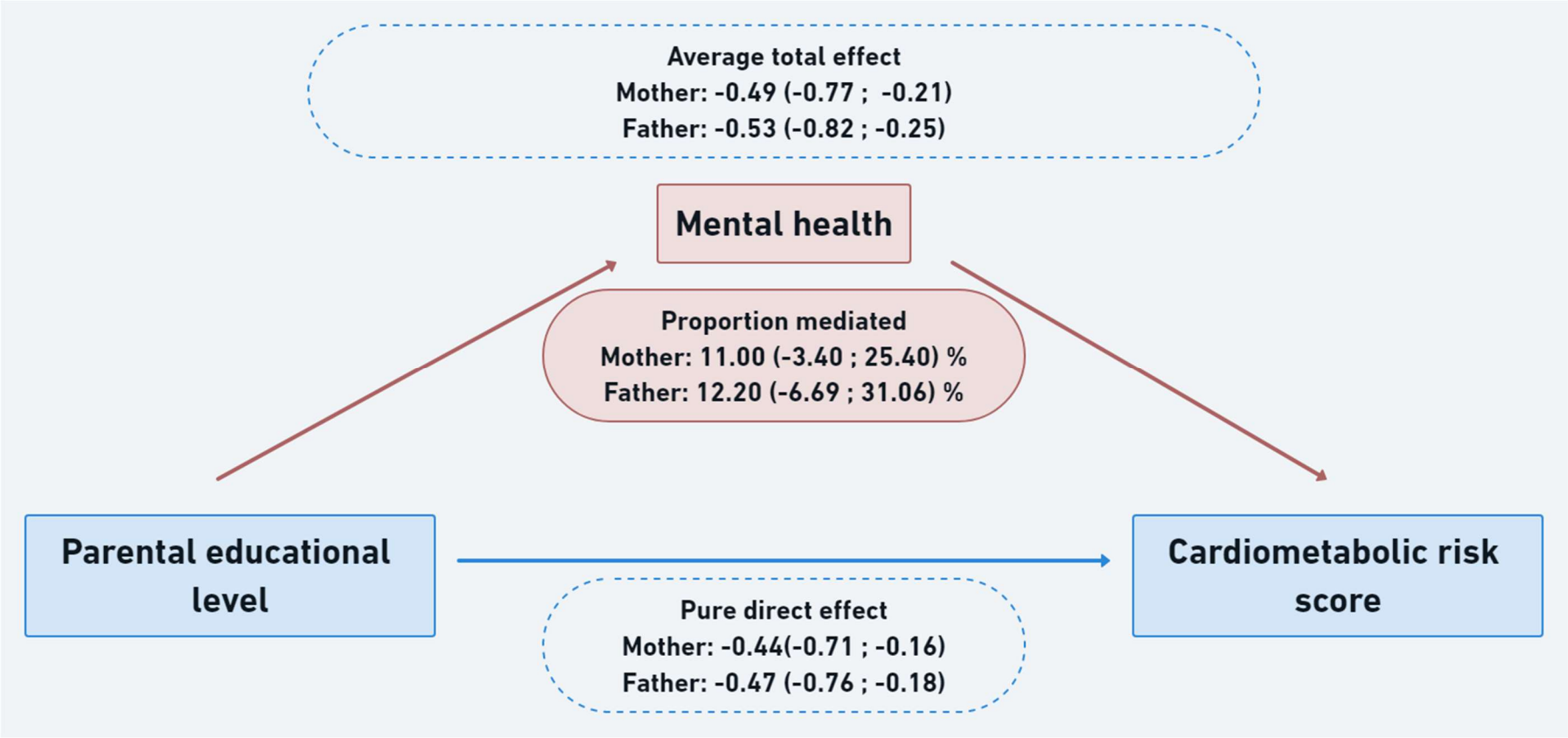
Risk marker	Men	Women
Cardiovascular		
Diastolic BP	0.39*	0.33*
Systolic BP	0.27	0.21
Heart rate	0.17	0.20
Total cholesterol	0.05	0.26
LDL-cholesterol	0.12	0.35*
Triglyceride	0.37*	0.43*
HDL-cholesterol	-0.42*	-0.37*
Coagulation factor 7	0.33*	0.15
Coagulation factor 11	0.36*	0.17
Metabolism		
Body fat percentage	0.85*	0.93*
Waist	0.90*	0.90*
HbA1c	0.32*	0.25
Insulin	0.63*	0.55*
Glucose	0.28	0.37*
Inflammation		
High-sensitive CRP	0.48*	0.64*
IL-6	0.31	0.62*
TNF-alpha	0.08	0.29
Interferon-gamma	0.04	0.06
Fibrinogen	0.45*	0.53*
ICAM-1	0.14	0.34*
VCAM-1	-0.08	-0.13
L-selectin	0.06	0.13
IL7R	-0.16	-0.21

Stars represent Bonferroni-corrected adjustment with p-values <0.05.

Appendix 7. Cardiometabolic risk score evaluated by four life course models with W_{12} applied, study 2

	Adjusted cardiometabolic risk score (95% confidence interval)			
		Educational level of the mother		
	N	**High**	**Average**	**Low**
The latent effects model (adjusted for adult SEP)				
Early childhood	*246*	**Ref**	-0.2 (-0.5;0.1)	0.2 (-0.1;0.6)
Middle childhood	*246*	**Ref**	-0.2 (-0.5;0.1)	0.3 (-0.1;0.6)
Late childhood	*249*	**Ref**	-0.2 (-0.5;0.1)	0.2 (-0.1;0.6)
The pathway model				
Prior to adjustment for lifestyle and adult SEP	*249*	**Ref**	-0.1 (-0.4;0.2)	**0.4 (0.0;0.7)**
After adjustment for lifestyle and adult SEP	*227*	**Ref**	-0.2 (-0.5;0.1)	0.2 (-0.1;0.6)
The social mobility model	*249*			
Separate upward mobility coefficient		**-0.4 (-0.8;0.0)**		
Separate downward mobility coefficient		0.1 (-0.4;0.6)		
The cumulative model	*246*			
Regression coefficient		**0.1 (0.0;0.1)**		

Appendix 8. The impact of mental health on the association between childhood SEP and cardiometabolic disease risk with W_{12} applied, study 3



Appendix 9. The association between subjective social status and cardiometabolic risk score in young adulthood with W_{12} applied, study 4

	Age 15						*Age 28*					
	Girls			**Boys**			**Women**			**Men**		
	n	**Low**	**High**	**n**	**Low**	**High**	**n**	**Low**	**High**	**n**	**Low**	**High**
Model 1	131	0.3 (-0.2 ; 0.9)	Ref	129	0.0 (-0.6 ; 0,6)	Ref	132	**1.0 (0.3 ; 1.6)**	Ref	132	**0.6 (0.1 ; 1.2)**	Ref
Model 2	130	0.3 (-0.3 ; 0.8)	Ref	129	0.1 (-0.5 ; 0.6)	Ref	130	**1.0 (0.3 ; 1.6)**	Ref	126	0.6 (-0.1 ; 1.3)	Ref
Model 3a	127	0.3 (-0.2 ; 0.8)	Ref	127	-0.2 (-0.7 ; 0.4)	Ref	127	**1.1 (0.5 ; 1,8)**	Ref	124	0.7 (0.0 ; 1,4)	Ref
Model 4a	-	-	-	-	-	-	127	**1.0 (0.4 ; 1,6)**	Ref	124	0.6 (-0.1 ; 1,3)	Ref
Model 3b	126	0.6 (0.0 ;1.1)	Ref	129	0.0 (-0.5 ; 0.6)	Ref	126	**0.9 (0.2 ; 1.5)**	Ref	126	0.6 (-0.1 ; 1,3)	Ref
Model 4b	-	-	-	-	-	-	126	**0.7 (0.1 ; 1.4)**	Ref	126	0.5 (-0.2 ;1.2)	Ref

All estimates are presented with 95% confidence intervals. P<0.0*5 compared to "high"* are marked with bold text.

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk)

Model 2: Model 1 + smoking and physical activity at age 15 and 28, respectively

Model 3a: Model 2 + educational level of the mother, Model 4a: Model 3a + adult educational level

Model 3b: Model 2 + childhood household income, Model 4b: Model 3b + adult educational level

Appendix 10. The association between subjective social status and cardiometabolic risk score in young adulthood with changed cut-point, study 4

	Age 15						*Age 28*					
	Girls			**Boys**			**Women**			**Men**		
	n	**Low**	**High**	**n**	**Low**	**High**	**n**	**Low**	**High**	**n**	**Low**	**High**
Model 1	131	0.6 (-0.6 ; 1.7)	Ref	129	-0.3 (-1.5 ; 0.8)	Ref	132	**1.4 (0.6 ; 2.2)**	Ref	132	0.7 (-0.3; 1.7)	Ref
Model 2	130	0.5 (-0.7 ; 1.7)	Ref	129	-0.4 (-1.4 ; 0.8)	Ref	130	**1.4 (0.5 ; 2.3)**	Ref	126	0.7 (-0.3 ; 1.7)	Ref
Model 3a	127	0.7 (-0.5 ; 1.8)	Ref	127	-0.4 (-1.5 ; 0.6)	Ref	127	**1.6 (0.5 ; 1.8)**	Ref	124	0.8 (-0.2 ; 1.8)	Ref
Model 4a	-	-	-	-	-	-	127	**1.2 (0.3 ; 2.2)**	Ref	124	0.7 (-0.2 ; 1.6)	Ref
Model 3b	126	0.7 (-0.5 ; 2.0)	Ref	129	-0.5 (-1.6 ; 0.6)	Ref	126	**1.2 (0.2 ; 2.3)**	Ref	126	0.7 (-0.4 ; 1.8)	Ref
Model 4b	-	-	-	-	-	-	126	0.8 (-0.2 ; 1.7)	Ref	126	0.7 (-0.4 ;1.7)	Ref

All estimates are presented with 95% confidence intervals. P<0.0*5 compared to "high"* are marked with bold text.

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk)

Model 2: Model 1 + smoking and physical activity at age 15 and 28, respectively

Model 3a: Model 2 + educational level of the mother, Model 4a: Model 3a + adult educational level

Model 3b: Model 2 + childhood household income, Model 4b: Model 3b + adult educational level

Papers

Papers

- **Paper1**

Paper 1

- **Paper 2**

Paper 2

- **Paper 3**

Paper 3

- **Paper 4**

Paper 4

Paper 1

Received: 17 February 2021 | Revised: 27 April 2021 | Accepted: 9 May 2021

DOI: 10.1002/osp4.528

ORIGINAL ARTICLE

Obesity Science and Practice Open Access WILEY

Traditional and novel cardiometabolic risk markers across strata of body mass index in young adults

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Funding information
The Karen Elise Jensen Foundation; Health Research Foundation of Central Denmark Region; Research Foundation GÃ,dstrup Hospital

Abstract

Background: Cardiometabolic risk increases with increasing body mass index (BMI). The exact mechanism is poorly understood, and traditional risk assessment of young adults with obesity has shown to be ineffective. Greater knowledge about potential new effective biomarkers and the use of advanced cardiac imaging for risk assessment in young adults is, therefore, necessary.

Objective: This study aims to explore traditional and novel cardiometabolic risk markers across strata of BMI in young adults.

Methods: Participants ($N = 264$, 50% women, age 28–30 years) were invited from an ongoing cohort study, based on BMI and sex. BMI-strata were: BMI <25, 25–30, >30 kg/m^2, representing normal weight (NW), overweight (OW), and obesity (OB). Participants underwent cardiac computed tomography to detect coronary artery calcification, measures of body composition, blood pressure measurements, and a comprehensive panel of circulating cardiometabolic risk markers.

Results: No significant coronary artery calcifications were detected in this study. Minor differences in median levels of traditional risk markers were detected across BMI-strata, for example, total cholesterol (men- NW: 4.7 (4.3–5.1) and OB: 4.8 (4.2–5.6) mmol/L, $p = 0.58$; women- NW: 4.3 (3.9–4.8) and OB: 4.7 (4.2–5.3) mmol/L, $p = 0.016$), whereas substantial differences were seen in markers of inflammation and glucose metabolism, for example, high sensitive CRP (men- NW: 0.6 (0.3–1.1) and OB: 2.8 (1.5–4.0) mg/L, $p < 0.001$; women- NW: 0.7 (0.3–1.7) and OB: 4.0 (2.2–7.8) mg/L, $p < 0.001$) and insulin (men- NW: 47.0 (35.0–59.0) and OB: 113.5 (72.0–151.0) pmol/L, $p < 0.001$; women- NW: 44.0 (35.0–60.0) and OB: 84.5 (60.0–126.0) pmol/L, $p < 0.001$).

Conclusion: In young adults, obesity is associated with an early onset insulin resistance and inflammatory response prior to development of coronary artery calcification and deterioration of lipid profiles.

KEYWORDS
body mass index, cardiovascular risk, inflammation, obesity, risk management

1 | INTRODUCTION

Obesity, physical inactivity, and diabetes mellitus are known risk factors for cardiovascular diseases (CVD). The prevalence rates for these risk factors continue to show a global increase.[1,2] Furthermore, age-specific analyses of prevalence and incidence for CVD suggest an increasing trend among individuals aged <55 years.[3–5] This is a major health concern as CVD is already the main cause of death in most developed countries.[6] Knowledge about which risk markers are present in young adulthood, and potentially could be incorporated into early risk assessment for CVD, is warranted to identify young individuals at high risk and to tailor effective strategies for CVD prevention.[7]

Due to the low chronological age and the slowly developing nature of CVD, most young individuals are currently classified as low risk according to established algorithms for CVD risk assessment involving traditional risk markers such as age, dyslipidemia, smoking, and hypertension.[8,9]

In addition to traditional risk markers, novel circulating biomarkers and coronary artery calcium score (CACS), evaluated by computed tomography (CT), have been suggested as potential refinements of the risk assessment.[10–13] For example, novel inflammatory biomarkers, most extensively high-sensitive CRP (hs-CRP) and various interleukins, are being evaluated both as risk markers and as mediators of disease progression, yet few studies have evaluated this in young adults and no specific anti-inflammatory treatment has been established.[14–23] Regarding CACS, little is known about the occurrence of CT positive plaques in young adults and CACS is currently not recommended in asymptomatic individuals.[7]

The aim of this study was to explore traditional and novel cardiometabolic risk markers across strata of sex and body mass index (BMI) in individuals aged 28–30 years. It was hypothesized that obesity was associated with increased values of circulating biomarkers, and that coronary artery calcification was more prevalent in young adults with obesity as compared to individuals with normal weight.

2 | MATERIALS AND METHODS

2.1 | Study population and overall design of the study

A flowchart of the sample selection is shown in Figure 1. The study participants were included from the ongoing West Jutland Cohort Study ($N = 3681$). The overall design and purpose of this study has been described elsewhere.[24,25] In brief, the West Jutland Cohort Study consists of all individuals born in 1989, living in a specific geographical area of Western Denmark in 2004. Participants filled in questionnaires at age 15 and at three follow-up time points (age 18, 21, and 28). At the latest follow-up, the participants were asked to indicate interest in a health examination. If interest was indicated, respondents were stratified into one of three BMI-groups of normal weight, overweight, and obesity (BMI < 25 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2) based on the latest self-reported height and weight. The participants were randomly sampled within their sex- and BMI-group and contacted through the nationally required electronic mailbox. A reminder was sent out to individuals not responding to the first invitation. Five consecutive waves of invitations were used, to obtain similar numbers in each sex- and BMI-group, until a total of 264 participants were included. Individuals with congenital heart disease, active cancer disease, severe claustrophobia, weight > 300 kg or who had not responded to both the initial and the latest questionnaire were excluded. Pregnant participants were included but investigated after giving birth (Figure 1). All data were linked to the unique personal identification number (CPR-number), assigned to all Danish citizens at birth and subsequently stored in the Danish Civil Registration System, to supplement the results with existing data from Danish registries.

2.2 | Assessing cardiovascular risk

The health examinations were performed from April 2018 to December 2019. All examinations were conducted in the morning and the participants were asked to avoid hard physical exercise, smoking, and more than two units of alcohol the day before and on the day of examination as well as to be fasting.

2.3 | Computed tomography of the heart

CACS was computed from ECG-gated cardiac CT scan (Toshiba Aquilion One, 320 slice CT scanner, Canon, Japan) using a standard clinical scan (120 keV and adjusted mAs). CACS was measured with the scoring system previously described by Agatston et al.[26] The system is semiautomatic and image analysis was blinded from all clinical information and evaluated by a trained physician. Additionally, an experienced CT cardiologist examined 15% randomly selected images, and 8% with uncertain primary evaluation.

2.4 | Blood sample collection, handling, and biochemical analyses

Fasting blood samples were obtained on the day of examination. All blood samples were drawn from an antecubital vein and handled according to standard operating procedures. The plasma and serum were stored at −80°C until batch analysis after inclusion of all participants. Samples were analyzed on different bioanalytical platforms. Eight biomarkers (HDL-cholesterol (HDL-C), total cholesterol, triglycerides, insulin, glucose, HbA1c, high-sensitive CRP (hs-CRP), and fibrinogen) were analyzed at the central laboratory at Aarhus University Hospital (Denmark). Four biomarkers (interleukin-6 (IL-6), interferon-γ (IFN-γ), interleukin-1beta (IL-1β), and tumor necrosis factor α (TNF-α)) were measured using Meso Scale Diagnostics technology V-plex human pro-inflammatory panel 1 (Meso Scale Diagnostics, Rockville, Maryland) at BioXpedia (Aarhus, Denmark) and six proteins (coagulation factor 7 + 11, Vascular Cell Adhesion

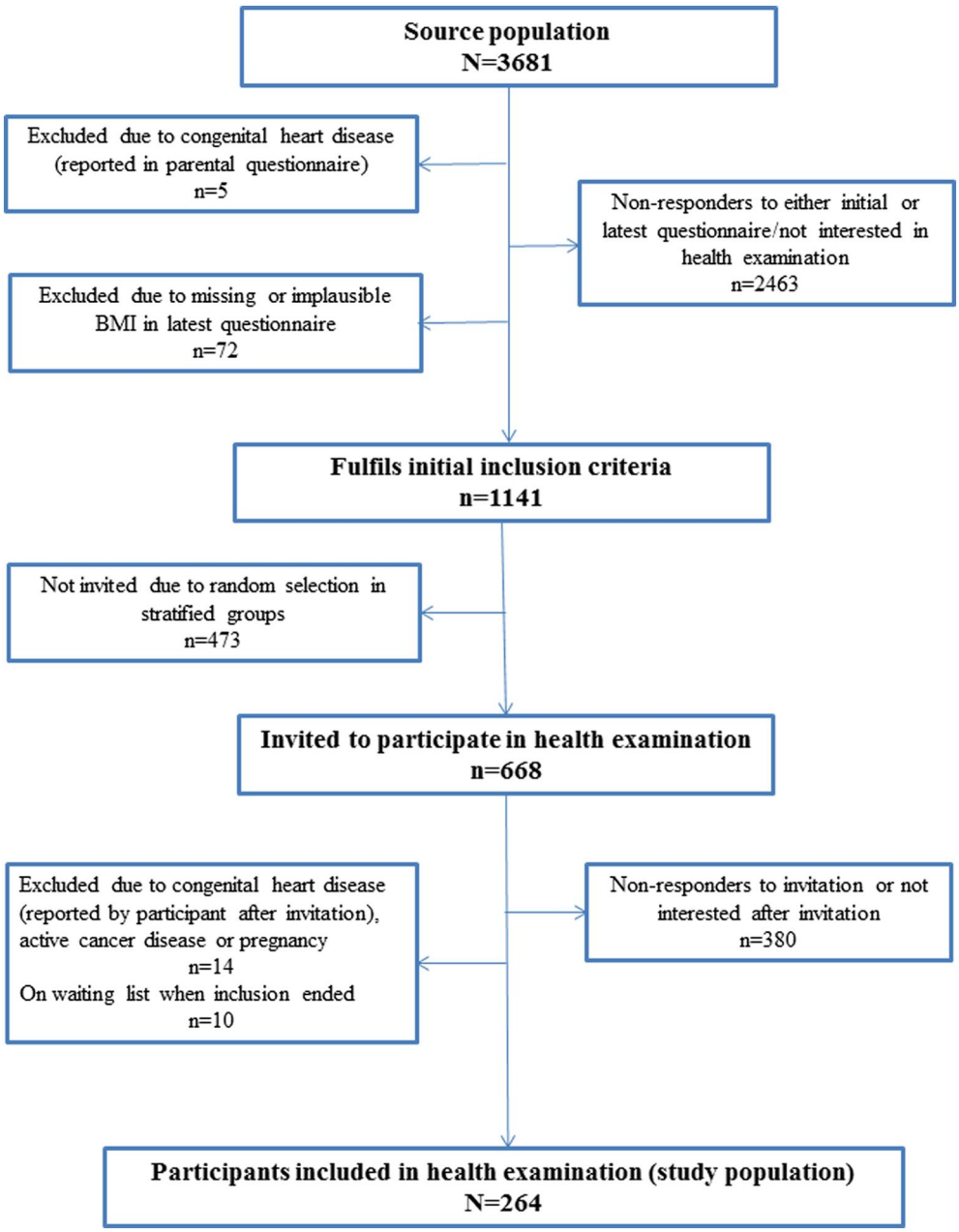

FIGURE 1 Flowchart of study population

Molecule 1 (VCAM-1), Intercellular Adhesion Molecule 1 (ICAM-1), L-selectin, and interleukin-7 receptor subunit alpha (IL7R-α)) were measured simultaneously using proximity extension assays from Olink (Olink Proteomics, Uppsala, Sweden) at BioXpedia (Aarhus, Denmark) using the protein panel CARDIOMETABOLIC (v.3603). Plasma LDL-cholesterol (LDL-C) was estimated by the Friedewald equation.[27]

2.5 | Measurements of weight, height, and waist circumference

Weight to the nearest 0.1 kg was measured using a calibrated electric scale with the participant wearing light clothes and no shoes. Standing height without shoes was recorded to the nearest 0.1 cm using a wall-mounted stadiometer. Waist (smallest circumference between the lower rib and iliac crest) circumference was measured in the horizontal plan using a narrow, nonelastic measuring tape after expiration.

2.6 | Bioelectrical impedance analysis

Whole-body measurements of body fat-percentage were obtained using a bioelectrical impedance analyzer (1500 MDD; 50 kHz, Bodystat, Isle of Man, United Kingdom) with skin surface electrodes located in pairs at the right wrist and ankle. Reliability of the

measurements was evaluated by three consecutive measurements in 5% of the participants. The mean difference from first to second and third measurement varied between 0 and 1%.

2.7 | Blood pressure measurements

Blood pressure was measured with a regularly calibrated automatic device. Mid-arm circumference was used to determine cuff-size. The cuff was applied in the sitting position and the participant was resting for 5 minutes before measurements. The participant was unable to see the monitor during measurements. Three measurements were recorded and the mean value of the last two readings was used to define diastolic and systolic blood pressures.

2.8 | Assessing lifestyle and parental history of cardiometabolic diseases

In addition to the questionnaires sent to the entire West Jutland Cohort, the 264 participants attending the health examination received a questionnaire concerning updated smoking status, medical history, and family occurrence of cardiometabolic diseases. Furthermore, parental cardiometabolic disease history from somatic public hospitals was obtained from Danish registries and combined with the questionnaire data. Parental disease history included diabetes (type 1 and 2) and CVD (ischemic heart disease, acute myocardial infarction, atherosclerosis, and stroke). Smoking was dichotomized into ever (former/current) or never smoker.

Information about physical activity was extracted from questionnaire data obtained at age 28. Based on the reported number of hours spent exercising each week, physical activity was divided into three categories of ≈0–0.5 h, ≈1–3 h, and ≥4 h.

2.9 | Statistical analysis

Statistical analyses were performed with the statistical software package Stata, version 16.0 and 16.1 (Stata Corporation, College Station, Texas, USA).

Nonfasting measurements of insulin and glucose were excluded from analyses. Participants with self-reported diabetes mellitus type 1 were excluded from insulin, glucose, and HbA1c analyses. Missing attendance to CT scan or answers to lifestyle questionnaires were excluded from analyses.

Normal distribution was visually evaluated by histograms and QQ plots and variance homogeneity was assessed by Bartlett's test. Due to skewness of the continuous data median values across BMI-strata for each sex were compared using Kruskal–Wallis test. Pearson's chi-squared test was used for categorical variables. Data are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables.

2.10 | Ethical considerations

The Danish Data Protection Agency, the Danish Medicines Board, and the National Committee on Health Research Ethics (no: 1-10-72-400-17) all approved the study. Participants signed a statement of consent prior to the health examination. The study complies with the Declaration of Helsinki.

3 | RESULTS

Seven participants had missing biomarker measurements due to technical issues, were not fasting at the time of blood collection, or had self-reported diabetes mellitus type 1. Nonattendance to the planned CT scan resulted in five missing results in this analysis and missing answers to the questionnaire regarding physical activity resulted in eight missing values.

The IL-1β measurements were below lower limit of quantification (0.646 pg/ml) in more than 98% of the samples and were, therefore, removed from the analysis.

3.1 | Sample characteristics

Table 1 summarizes sex- and BMI-stratified biomarker values and additional characteristics. A total of 264 (50% women, age 28–30 years) participants were included in the study. There were no differences across BMI-strata regarding self-reported physical activity. Men with obesity smoked more compared to men with normal weight but no statistical significant difference was observed across BMI-groups for women. Participants with overweight or obesity more often had parents with cardiometabolic diseases as compared to participants with normal weight.

As seen in Figure 2, body fat percentage (men: 17.0 (15.0–19.0), 20.1 (18.0–22.0), and 29.3 (26.1–32.6) %, $p < 0.001$; women: 25.9 (23.6–29.1), 34.1 (31.0–36.4), and 44.5 (39.3–46.0) %, $p < 0.001$) and waist circumference (men: 82.5 (79.0–87.0), 90.5 (87.0–96.0), and 110.0 (105.0–117.0) cm, $p < 0.001$; women: 73.5 (69.5–87.0), 85.0 (81.0–88.0), and 99.0 (93.0–107.0) cm, $p < 0.001$) varied across strata of sex and BMI.

3.2 | Coronary artery calcification

There was a low occurrence of coronary artery calcification detected by cardiac CT. No participant had a CACS > 5 and all men with overweight and obesity as well as all women had CACS = 0 (Table 1).

3.3 | Cardiovascular profile, men

As seen in Table 1, men with obesity had higher systolic (129 (122–136) vs. 123 (114–131) mmHg) and diastolic (81 (73–86) vs. 73 (66–78)

TABLE 1 Median biomarker values and additional characteristics by body mass index and sex

		Men			Women		
	N	Normal weight	Overweight	Obesity	Normal weight	Overweight	Obesity
Total	264	38 (29%)	58 (44%)	36 (27%)	40 (30%)	45 (34%)	47 (36%)
BMI (kg/m^2)	264	23.0 (22.0–24.1)	26.8 (26.0–28.1)	34.4 (32.0–37.2)	22.2 (20.7–23.5)	27.6 (26.2–28.6)	35.1 (32.5–37.9)
Lifestyle							
Smoking	264						
Never		29 (76%)	37 (64%)	19 (53%)*	32 (80%)	31 (69%)	30 (64%)
Ever		9 (24%)	21 (36%)	17 (47%)*	8 (20%)	14 (31%)	17 (36%)
Physical activity	256						
0–0.5 h/week		10 (27%)	13 (23%)	7 (22%)	7 (18%)	8 (18%)	13 (28%)
1–3 h/week		14 (38%)	23 (40%)	14 (44%)	22 (55%)	24 (55%)	26 (57%)
>4 h/week		13 (35%)	21 (37%)	11 (34%)	11 (28%)	12 (27%)	7 (15%)
Family disease							
Parental diabetic disease	264	0 (0%)	6 (10%)*	10 (28%)**	<5	6 (13%)	14 (30%)*
Parental cardiovascular disease	264	8 (21%)	14 (24%)	13 (36%)	7 (18%)	17 (38%)*	19 (40%)*
Cardiovascular							
CACS > 0	259	<5	0	0	0	0	0
Diastolic blood pressure mmHg	264	73 (66–78)	74 (69–80)	81 (73–86)**	73 (69–76)	74 (69–77)	77 (73–85)*
Systolic blood pressure (mmHg)	264	123 (114–131)	125 (120–132)	129 (122–136)*	112 (104–118)	113 (105–121)	116 (109–120)
Resting heart rate (beats/min)	264	62 (53–70)	60 (49–65)	64 (56–72)	62 (57–66)	61 (56–66)	66 (58–74)*
Total cholesterol (mmol/L)	264	4.7 (4.3–5.1)	4.6 (4.1–5.2)	4.8 (4.2–5.6)	4.3 (3.9–4.8)	4.6 (4.1–5.2)	4.7 (4.2–5.3)*
LDL-cholesterol (mmol/L)	263	2.8 (2.4–3.1)	2.8 (2.4–3.3)	3.0 (2.5–3.4)	2.3 (1.9–2.8)	2.7 (2.4–3.1)*	2.8 (2.4–3.2)**
Triglyceride (mmol/L)	264	0.9 (0.7–1.5)	1.1 (0.8–1.4)	1.4 (1.1–2.0)**	0.8 (0.7–1.0)	0.9 (0.7–1.1)	1.2 (0.9–1.6)**
HDL-cholesterol (mmol/L)	264	1.3 (1.2–1.6)	1.3 (1.1–1.5)	1.1 (1.0–1.2)**	1.6 (1.4–1.7)	1.4 (1.2–1.6)	1.3 (1.1–1.4)**
Coagulation factor 7 NPX	262	4.2 (4.0–4.4)	4.4 (4.0–4.5)	4.4 (4.1–4.8)*	4.4 (4.1–4.6)	4.4 (4.1–4.6)	4.5 (4.2–4.8)
Coagulation factor 11 NPX	262	6.9 (6.8–7.1)	7.0 (6.7–7.2)	7.2 (6.9–7.3)**	6.9 (6.8–7.2)	7.0 (6.9–7.2)	7.0 (6.9–7.3)
Metabolism							
Body fat-percentage (%)	263	17.0 (15.0–19.0)	20.1 (18.0–22.0)**	29.3 (26.1–32.6)**	25.9 (23.6–29.1)	34.1 (31.0–36.4)**	44.5 (39.3–46.0)**
Waist (cm)	264	82.5 (79.0–87.0)	90.5 (87.0–96.0)**	110.0(105.0–117.0)**	73.5 (69.5–78.0)	85.0 (81.0–88.0)**	99.0 (93.0–107.0)**
HbA1C (mmol/mol)	262	31.1 (29.6–32.8)	31.1 (29.9–33.1)	32.7 (31.4–35.0)*	30.3 (28.7–32.9)	31.4 (28.8–32.1)	32.3 (30.5–34.4)*
Insulin (pmol/L)	262	47.0 (35.0–59.0)	52.5 (42.0–66.0)*	113.5 (72.0–151.0)**	44.0 (35.0-60.0)	61.0 (42.0–83.0)*	84.5 (60.0–126.0)**
Glucose (mmol/L)	262	4.9 (4.6–5.2)	5.0 (4.7–5.3)	5.1 (4.8–5.5)*	4.5 (4.4–4.8)	4.7 (4.4–4.9)	4.9 (4.7–5.1)**

(Continues)

TABLE 1 (Continued)

		Men			Women		
	N	Normal weight	Overweight	Obesity	Normal weight	Overweight	Obesity
Inflammation							
High-sensitive CRP (mg/L)	264	0.6 (0.3–1.1)	0.7 (0.4–1.7)	2.8 (1.5–4.0)**	0.7 (0.3–1.7)	1.8 (0.9–3.7)**	4.0 (2.2–7.8)**
IL-6 (pg/ml)	264	0.3 (0.3–0.5)	0.4 (0.3–0.5)	0.6 (0.4–0.9)**	0.3 (0.2–0.4)	0.5 (0.3–0.8)**	0.8 (0.6–1.1)**
TNF-α (pg/ml)	264	2.6 (2.1–3.1)	2.5 (2.1–2.8)	2.6 (2.3–3.1)	2.2 (1.9–2.9)	2.5 (2.1–2.8)	2.7 (2.4–3.2)**
IFN-γ (pg/ml)	264	4.9 (3.3–7.0)	4.0 (3.1–7.6)	4.9 (3.2–6.2)	4.1 (3.2–6.3)	4.9 (3.5–7.7)	4.9 (3.4–7.9)
Fibrinogen (μmol/L)	263	7.0 (6.1–8.1)	7.4 (6.6–8.4)	8.9 (7.7–9.9)**	8.7 (7.4–9.3)	9.0 (8.1–9.9)	11.2 (9.3–12.6)**
ICAM1 NPX	262	6.4 (6.2–6.5)	6.4 (6.2–6.6)	6.5 (6.3–6.7)	6.3 (6.2–6.5)	6.4 (6.1–-6.5)	6.5 (6.4–6.7)**
VCAM1 NPX	262	4.7 (4.6–4.8)	4.7 (4.5–4.9)	4.7 (4.5–4.8)	4.8 (4.6–5.0)	4.6 (4.4–4.8)*	4.7 (4.5–4.9)
L-selectin NPX	262	9.2 (9.0–9.4)	9.2 (9.1–9.4)	9.2 (9.0–9.4)	9.2 (9.1–9.5)	9.2 (9.1–9.4)	9.3 (9.2–9.5)
IL7R NPX	262	2.2 (1.9–2.7)	2.2 (1.9–2.6)	2.1 (1.6–2.5)	2.2 (1.9–2.5)	2.0 (1.8–2.2)	1.8 (1.4–2.3)*

Note: Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2). Values are shown as median (interquartile range) for continuous data and number (percentage) for categorical variables.

Abbreviations: BMI, body mass index; CACS, coronary artery calcification score; ICAM1, intercellular adhesion molecule 1; IFN-γ, interferon-gamma; IL-6, interleukin 6; IL7R, interleukin-7 receptor subunit alpha; NPX, normalized protein expression values (arbitrary unit in Log 2 scale); TNF-α, tumor necrosis factor alpha; VCAM1, vascular cell adhesion molecule 1.

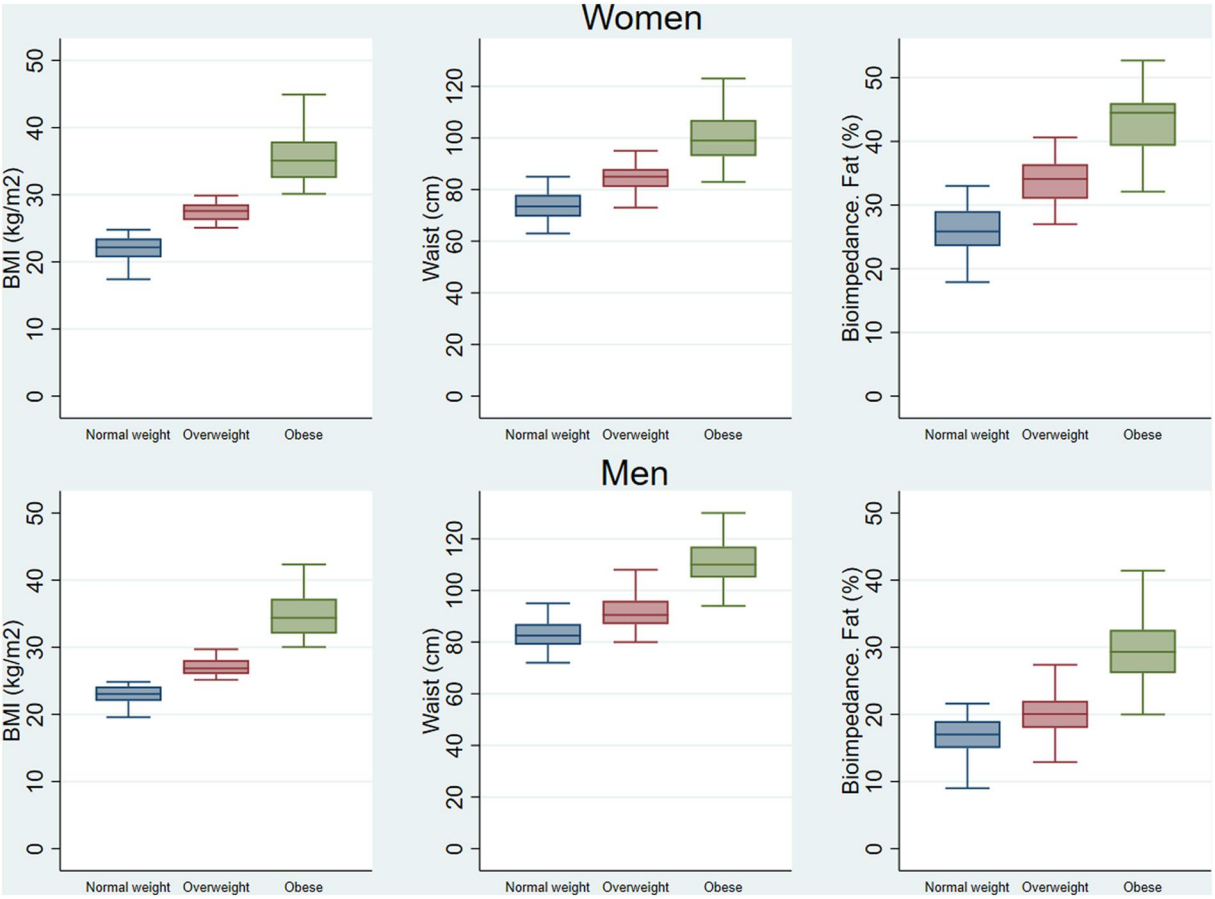

FIGURE 2 Body composition by body mass index (BMI) stratum and sex. Box plot bordered at the upper and lower quartiles of biomarker value. Whiskers extend from the most extreme values within 1.5*inter-quartile-range of the nearest quartile. Outside values excluded. All *p*-values for the overall comparison between BMI-groups are <0.001. *P*-values are conducted from Kruskal–Wallis test. Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2)

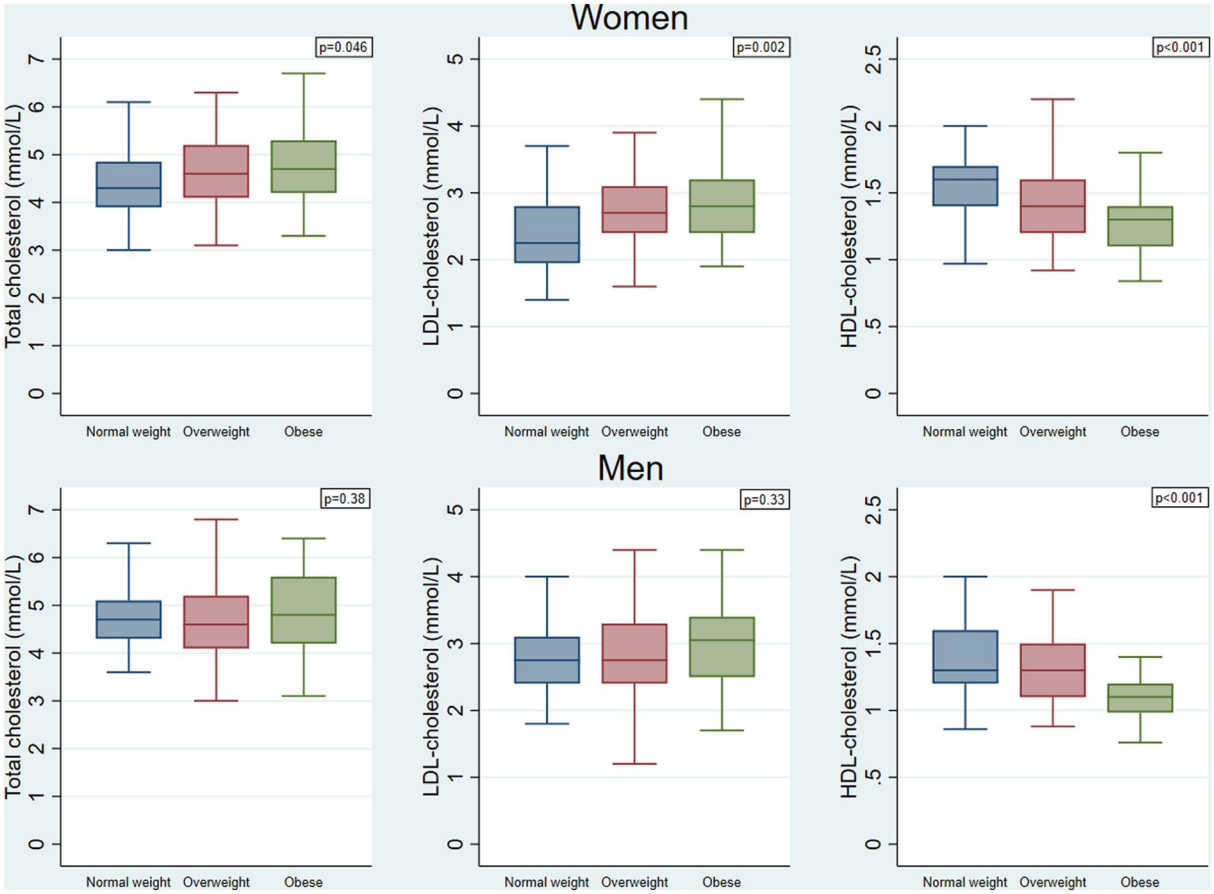

FIGURE 3 Selected biomarkers by body mass index stratum (BMI) and sex. Box plot bordered at the upper and lower quartiles of biomarker value. Whiskers extend from the most extreme values within 1.5*inter-quartile-range of the nearest quartile. Outside values excluded. *P*-values for the overall comparison between BMI-groups are conducted from Kruskal–Wallis test. Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2)

mmHg) blood pressures, higher levels of triglycerides (1.4 (1.1–2.0) vs. 0.9 (0.7–1.5) mmol/L), and lower levels of HDL-C (1.1 (1.0–1.2) vs. 1.3 (1.2–1.6) mmol/L) compared to participants with normal weight (Figures 3 and 4). On the contrary, total cholesterol (4.7, 4.6, and 4.8 mmol/L, $p = 0.38$) and LDL-C (2.8, 2.8, and 3.0 mmol/L, $p = 0.33$) were similar across BMI-strata (Figure 3).

3.4 | Cardiovascular profile, women

Table 1 also shows that higher systolic (116 (109–120) vs. 112 (104–118) mmHg) and diastolic (77 (73–85) vs. 73 (69–76) mmHg) blood pressures, higher levels of triglycerides (1.2 (0.9–1.6) vs. 0.8 (0.7–1.0) mmol/L), total cholesterol (4.7 (4.2–5.3) vs. 4.3 (3.9–4.8) mmol/L), and lower levels of HDL-C (1.3 (1.1–1.4) vs. 1.6 (1.4–1.7) mmol/L) were seen comparing women with obesity to women with normal weight (Figures 3 and 4). A similar tendency was seen comparing women with overweight to women with normal weight, though not reaching statistical significance. Furthermore, statistical significant higher levels of LDL-C were seen comparing women with obesity (2.8 (2.4–3.2) vs. 2.3 (1.9–2.8) mmol/L) and women with overweight (2.7 (2.4–3.1) vs. 2.3 (1.9–2.8) mmol/L) to women with normal weight but not comparing women with overweight to women with obesity ($p = 0.46$) (Figure 3).

3.5 | Metabolic profile, men and women

As can be seen in Table 1, the median level of HbA1c were higher among participants with obesity (men: 32.7 (31.4–35.0) vs. 31.1 (29.6–32.8) mmol/mol; women 32.3 (30.5–34.4) vs. 30.3 (28.7–32.9) mmol/mol) but not participants with overweight (men: 31.1 (29.9–33.1) vs. 31.1 (29.6–32.8) mmol/mol; women: 31.4 (28.8–32.1) vs. 30.3 (28.7–32.9) mmol/mol) compared to participants with normal weight. Furthermore, median insulin level was almost doubled among women with obesity and more than doubled among men with obesity compared to the groups with normal weight. A smaller but statistically significant difference in median insulin levels was also seen comparing participants with overweight to participants with normal weight in both sexes (Figure 4). Glucose levels were higher among participants with obesity (men: 5.1 (4.8–5.5) vs. 4.9 (4.6–5.2) mmol/L; women: 4.9

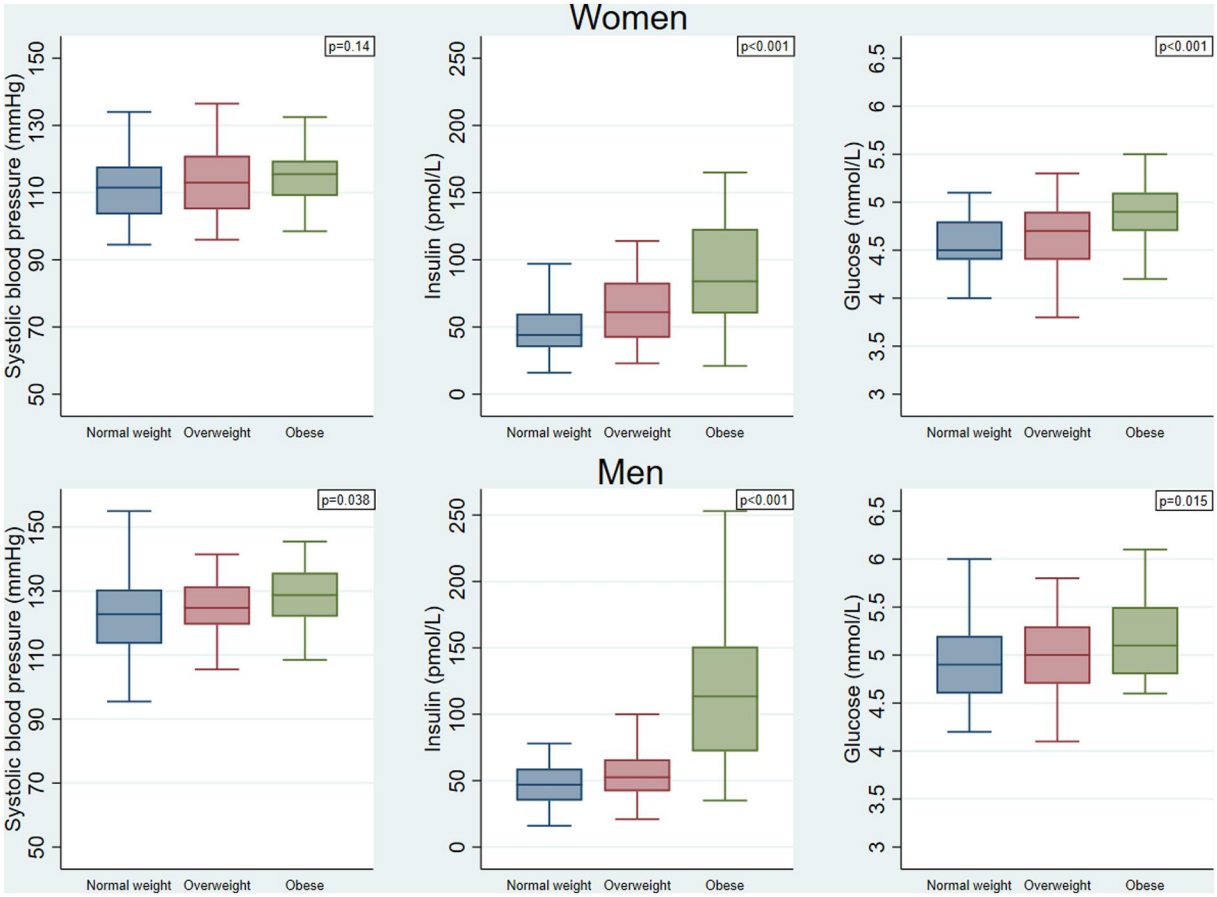

FIGURE 4 Selected biomarkers by body mass index (BMI) stratum and sex. Box plot bordered at the upper and lower quartiles of biomarker value. Whiskers extend from the most extreme values within 1.5*inter-quartile-range of the nearest quartile. Outside values excluded. *P*-values for the overall comparison between BMI-groups are conducted from Kruskal–Wallis test. Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2)

(4.7–5.1) vs. 4.5 (4.4–4.8) mmol/L) but not overweight of both sexes compared to participants with normal weight (Figure 4).

3.6 | Inflammatory profile, men and women

Differences in median levels of hs-CRP (men: >4-fold, women: almost 6-fold) and IL-6 (>2-fold for both sexes) were seen for participants with obesity compared to participants with normal weight (Table 1, Figure 5). Similarly, median levels of fibrinogen were higher comparing participants with obesity to participants with normal weight (men: 8.9 (7.7–9.9) vs. 7.0 (6.1–8.1) μmol/L; women: 11.2 (9.3–12.6) vs. 8.7 (7.4–9.3) μmol/L). On the contrary, no significant differences were observed in median levels of IFN-γ comparing participants with overweight (men: $p = 0.38$; women: $p = 0.21$) and obesity (men: $p = 0.52$; women: $p = 0.093$) to participants with normal weight. Women with obesity ($p < 0.001$), but not women with overweight ($p = 0.081$), men with overweight ($p = 0.42$) or men with obesity ($p = 0.67$) had higher median levels of TNF-α compared to the groups with normal weight.

4 | DISCUSSION

This study investigated a wide range of traditional and novel cardiometabolic risk markers in 264 young adults, aged 28–30 years, across strata of BMI and sex. The overall finding is that there was no clinically significant coronary artery calcification on cardiac CT scans in any of the participant strata. Furthermore, we found minor or insignificant differences across male BMI-groups in traditional risk markers like LDL-C and total cholesterol. As opposed to this, there were striking variations in other biomarkers related to glucose-metabolism and inflammation like insulin, hs-CRP, fibrinogen, and IL-6 across sex-stratified BMI-groups.

Knowledge on CACS in asymptomatic individuals below 30 years of age is scarce. One of the few studies to asses CACS in young adults is the CARDIA study.[28] In this follow-up study, 5115 participants (18–30 years at inclusion) were enrolled and followed. The study demonstrated a prevalence of CACS > 0 in 10% of participants at a mean age of 40.3 years and that any degree of plaque was associated with increased risk of coronary events over a mean follow-up period of 12.5 years. Furthermore, the study found progression of CAC over

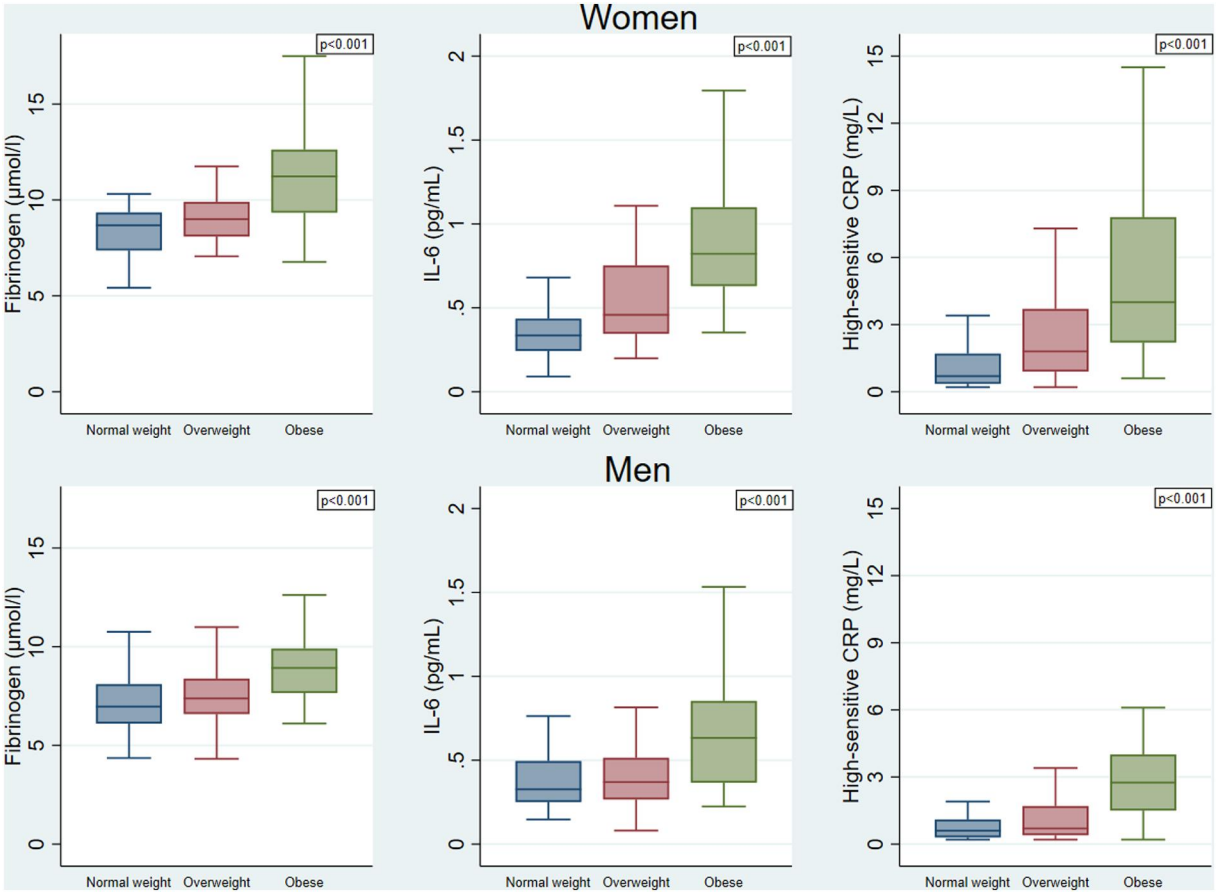

FIGURE 5 Selected biomarkers by body mass index (BMI) stratum and sex. Box plot bordered at the upper and lower quartiles of biomarker value. Whiskers extend from the most extreme values within 1.5*inter-quartile-range of the nearest quartile. Outside values excluded. *P*-values for the overall comparison between BMI-groups are conducted from Kruskal–Wallis test. Normal weight (BMI < 25 kg/m^2), overweight (BMI 25–30 kg/m^2), and obesity (BMI > 30 kg/m^2)

a 5-year period in 14.4% of middle-aged adults with CACS = 0 at the initial scan. Newly published studies from the CAC consortium, an ongoing multicenter study, demonstrated increased prevalence of CAC in individuals with overweight and obesity compared to individuals with normal weight, and an overall CAC prevalence of 21.8% in individuals aged 30–39 years.[29,30] The CAC consortium study population was asymptomatic; however, had clinical indications for CAC scoring, most often hyperlipidemia or a family history of CVD, which might explain the high occurrence of elevated CACS. The Bogalusa Heart study described the prevalence of fatty streaks and fibrous plaques in childhood and young adulthood by autopsy studies performed on individuals who had died from various causes, mostly accident or homicide.[31] The prevalence of fatty streaks was 85% at age 21–39 years and the prevalence of fibrous plaque lesions in the coronary arteries was 69% at age 26–39 years. Traditional cardiovascular risk factors such as BMI, lipids, and blood pressure were strongly associated with the amount of lesions. The Muscatine Study investigated a representative sample of a cohort from Iowa, and demonstrated increased carotid intima media thickness in adults aged 33–42 years with increased levels of total cholesterol in childhood and 21% with CAC at age 29–37.[32,33] Overall, it would be expected to find some degree of coronary calcification in the present study. CAC measured by CT is considered a reliable, noninvasive technique to evaluate coronary plaque burden associated with cardiovascular events.[34] It does, however, not evaluate noncalcified plaques or increased intima media thickness. Taken together with previous research, the findings seem to indicate that below 30 years of age only soft noncalcified plaques are evident, despite having a high-risk profile measured by multiple other parameters.

This study supports the association of higher levels of IL-6, fibrinogen, hs-CRP, and to some degree TNF-α with higher BMI. However, lowering of LDL-C is the primary aim of lipid-lowering therapy and only insignificant differences across male BMI-strata were seen in the current study. This emphasizes the question about the role of inflammation in CVD; inflammation could be causatively related to atherosclerosis or merely a risk marker which is not involved in the pathogenesis. The Jupiter trial evaluated apparently healthy individuals with low LDL-C but increased hs-CRP to see if vascular protection was achieved by statin treatment in the absence of hypercholesterolemia. The researchers found a reduction in both LDL-C and hs-CRP and a 44% reduction in all vascular events.[35] This does not answer the question on a causative role of inflammation as

reduced hs-CRP could potentially be secondary to reduced LDL-C. However, based on the overall high-risk profile of the groups with obesity in the present study, the findings support a more sophisticated risk assessment of young individuals including inflammatory markers, independently of levels of LDL-C and total cholesterol.

The observed more than twofold level of insulin in participants with obesity compared to participants with normal weight is striking, in particular in light of the normal levels of HbA1c. These findings indicate that abnormal insulin-desensitizing signals from target tissues has initiated but widespread impaired glucose homeostasis is not yet complete. Prior studies have furthermore shown that increased levels of TNF-α and IL-6 may be related to insulin resistance and this association, together with the association between hyperinsulinemia and CVD endpoints, need further investigation.[36,37]

4.1 | Limitations

The study is descriptive in nature and does not document any causal pathways between obesity and CVD risk. The biomarkers measured in this study can be both an antecedent and a consequence of each other. However, multiple and overlapping biomarkers involved in cardiovascular, metabolic, and inflammatory status were performed to strengthen the results. This study only investigated calcified lesions at the low dose CT scan. Supplementary noninvasive image modalities would be necessary to evaluate noncalcified plaques, intima media thickness, or pericardial fat depositions which could be of interest in this young population.

Epidemiological challenges concerning participation should also be mentioned. Responders to questionnaires generally have higher socioeconomic position and better health. A former study investigating the initial nonparticipation in the West Jutland Cohort study revealed that nonresponders were more likely to come from families with lower income and educational levels.[25] Further selection on most healthy individuals wanting to participate in a clinical examination is possible; however, this was accounted for by BMI-stratified inclusion and reliability of this selection was supported by measurements of body composition. Supplementary analyses (not shown) on self-reported lifestyle factors (smoking and physical activity), register based educational level at age 28, and parental cardiometabolic diseases revealed no statistically significant differences in sex- and BMI-stratified groups comparing study participants with nonparticipating responders to the latest questionnaire. Furthermore, the narrow age range of participants insure that no age effect can confound the variation in biomarker levels across BMI.

5 | CONCLUSION

In conclusion, increased BMI in young adults seems to be associated with only slightly increased levels of clinically used risk markers while several novel cardiometabolic biomarkers were markedly elevated. Cardiac CT detected no clinically significant coronary artery calcification in any of the participants. These findings support the hypothesis of an early onset insulin resistance and inflammatory response to obesity leading to increased cardiometabolic risk. CACS-screening in young, asymptomatic individuals does not seem justified based on these results but the findings hold promise that intervention at early age can precede formation of calcified plaques in the coronary arteries. A more sophisticated risk assessment, including novel cardiometabolic biomarkers, could be considered to improve preventive strategies of obesity-related CVD at this early stage.

ACKNOWLEDGMENTS

The authors want to thank all study participants and the study nurses, radiographers, and secretaries at Cardiovascular Research Unit, Departments of Cardiology and Radiology, Regional Hospital West Jutland, Denmark. We also acknowledge the contribution of Jesper Medom Vestergaard for his assistance with data management. The Karen Elise Jensen Foundation, Health Research Foundation of Central Denmark Region, and the Research Foundation Gødstrup Hospital contributed to the funding of the study. None of the funding organizations had any influence on study design, analysis, or interpretation of data.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Mia Klinkvort Kempel, Trine Nøhr Winding, Johan Hviid Andersen, and Morten Böttcher contributed to the conception and design of the work. All authors contributed to the acquisition and interpretation of data. Mia Klinkvort Kempel analyzed the data and drafted the manuscript. All critically revised the manuscript and gave final approval.

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How to cite this article: Kempel MK, Winding TN, Lynggaard V, Brantlov S, Andersen JH, Böttcher M. Traditional and novel cardiometabolic risk markers across strata of body mass index in young adults. *Obes Sci Pract*. 2021;1–11. https://doi.org/10.1002/osp4.528

Paper 2

BMC Public Health

RESEARCH

Open Access

Evaluating the association between socioeconomic position and cardiometabolic risk markers in young adulthood by different life course models

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Abstract

Background: Cardiometabolic health in adulthood is associated with socioeconomic position (SEP) in childhood. Although this has been studied by previous research several questions need to be addressed. E.g. knowledge about the association with timing, extent of the exposure as well as lifestyle and adult SEP, is essential to address the increasing social gradient in cardiometabolic diseases.

Methods: This study included a sub-sample ($N = 264$, 50% women, age 28–30) from an ongoing cohort study. We used a combination of national registers, longitudinal questionnaire data and clinical data. We examined the association between childhood SEP and cardiometabolic risk, measured by a score of multiple risk markers in young adulthood. SEP-indicators included mother's educational level and household income. The association was evaluated by four different life course models; the latent effects model, the pathway model, the cumulative model and the social mobility model.

Results: We found an inverse association between mother's educational level and cardiometabolic risk. The association was statistically significant evaluated by the pathway and cumulative life course models, however statistically insignificant evaluated by the latent effects model. No specific association with social mobility was observed. However, high adult educational level seems to have a protecting impact on the association. No association was found between household income and cardiometabolic risk in any of the applied life course models.

Conclusion: Low childhood SEP, represented by mother's educational level but not household income, is associated with increased cardiometabolic risk in young adulthood. The accumulation of exposure, lifestyle and adult educational attainment are important for the association. In contrast, intergenerational social mobility does not seem to have a specific impact on the association and we find no evidence for a particular timing in childhood.

Keywords: Socioeconomic position, Social mobility, Lifestyle, Life course models, Cardiometabolic diseases, Epidemiology

Background

Several studies have found an inverse association between socioeconomic position (SEP) in childhood and cardiometabolic diseases in adulthood [1–4]. However, many studies are cross-sectional, measuring SEP in adulthood at one time-point and assessing

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childhood SEP by retrospective self-reporting [4–7]. Moreover, SEP is a wide-ranging concept measured by various indicators, e.g. household income, educational attainment or occupation, with different impact and potentials for intervention. None of these indicators are stationary, and the influence of duration, timing and modifiability in the association with later health outcomes are not fully understood [8].

Four different frameworks try to capture this in life course research [9–11]. Investigating multiple life course models simultaneously utilizing the same data allows for a better comparison of how well each model describes the observed association. A simplified illustration of the four life course models are presented in Fig. 1.

The latent effects model evaluates certain critical/sensitive periods believed to have either irreversible or highly profound impact on the outcome of interest [12, 13]. Both early, middle and late childhood are mentioned as powerful periods due to neurobiological and social developmental processes that might influence the individual for life [14, 15].

The pathway model evaluates a continuity of circumstances from early life onwards. The life course is seen as a path where one life circumstance leads to the next as a trajectory of (dis) advantage [12, 16]. Not only the initial exposure but also later experiences are of interest. All elements on the path, including behavioural factors, should be included when empirically examining this model [9].

The cumulative model evaluates the overall accumulation of exposure across the lifespan, regardless of timing. Some researchers describe it as "health capital" that influences current and future disease risk [13, 17].

The social mobility model evaluates the effects of intergenerational social mobility, i.e. moving upwards or downwards on the social ladder from one position at origin to another at destination. Studies are inconsistent and four conflicting theories exist with regard to health effects of social mobility; The first suggests negative effects of any kind of mobility from increased psychological stress due to transition from one position in society to another [18]. The second suggests positive effects of upward social mobility due to a new sense of control and boosting of well-being [19]. The third suggests negative health effects of downward mobility due to the stress and feeling of unjust that emerge when accepting a new lower position [20]. The fourth is the "acculturation thesis" that focuses on the ability of mobile individuals to adapt to new environments rather than any additional effects of mobility per se [21].

The four frameworks thus focus on different consequences of the exposure to low childhood SEP: Specific timing of exposure with lasting impact independent of later experiences (evaluated by the latent effects model), the duration of the exposure independent of timing (evaluated by the cumulative model), and the later effects of the exposure (evaluated by the pathway model and social mobility model). These frameworks are often seen as competing models but prior research suggests an interdependent nature of the models and encourages the inclusion of multiple models when analysing life course perspectives in health [9, 22].

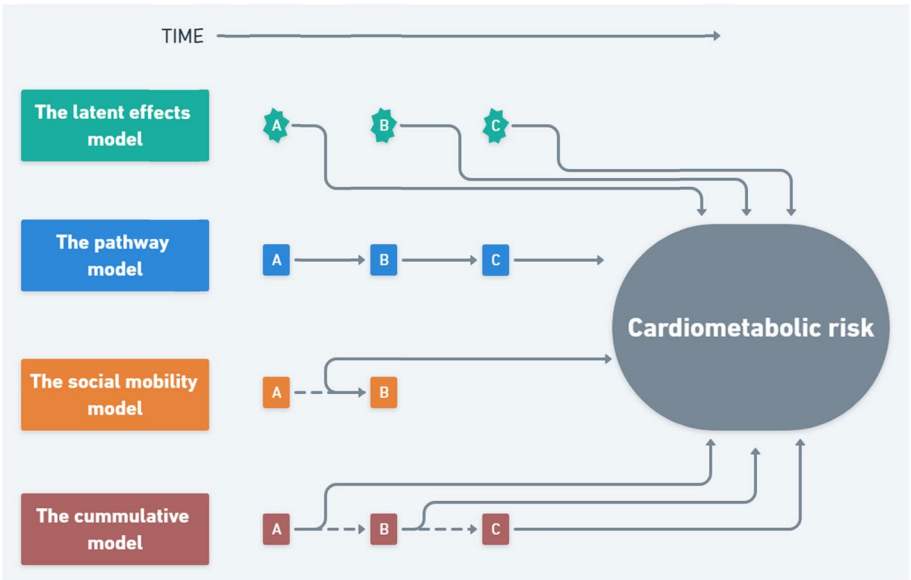

Fig. 1 Simplified illustration of the four life course models

Furthermore, there is an ongoing debate regarding the best way to define measures of cardiometabolic risk in young individuals prior to manifest disease [23, 24]. Most agree that clusters of specific cardiometabolic risk markers tend to co-exist. Consequently, recent work recommends the use of multiple risk markers and continuous scales to avoid specific thresholds and to account for the interplay between different pathological domains (e.g. related to inflammation, metabolism, dyslipidaemia and thrombosis) [23–25].

In order to fill in gaps in the knowledge identified by prior research, this study was conducted to investigate the association between childhood SEP, measured prospectively by different indicators, and cardiometabolic disease risk, measured by multiple risk markers in young adulthood, within each of the four life course frameworks.

Methods

Study population

This study included a sub-sample ($N=264$, 50% women, age 28–30 years) from the ongoing West Jutland Cohort Study ($N=3681$). The West Jutland Cohort consists of all individuals born in 1989, living in a specific county in Denmark in 2004. Participants were invited to fill in questionnaires at ages 15, 18, 21 and 28 years. In the latest questionnaire the participants had the opportunity to indicate interest in a health examination. If interest was indicated, and they had also filled in the initial questionnaire, they were invited into the sub-sample. They were invited based on sex and latest self-reported Body Mass Index (BMI) to obtain similar numbers in each sex- and BMI-group of individuals with normal weight, overweight and obesity (BMI <25, 25–30 and $>30\,kg/m^2$), until a total of 264 participants were included (Fig. 2). Questionnaire- and clinical data were linked to high-quality national register data from Statistics Denmark,

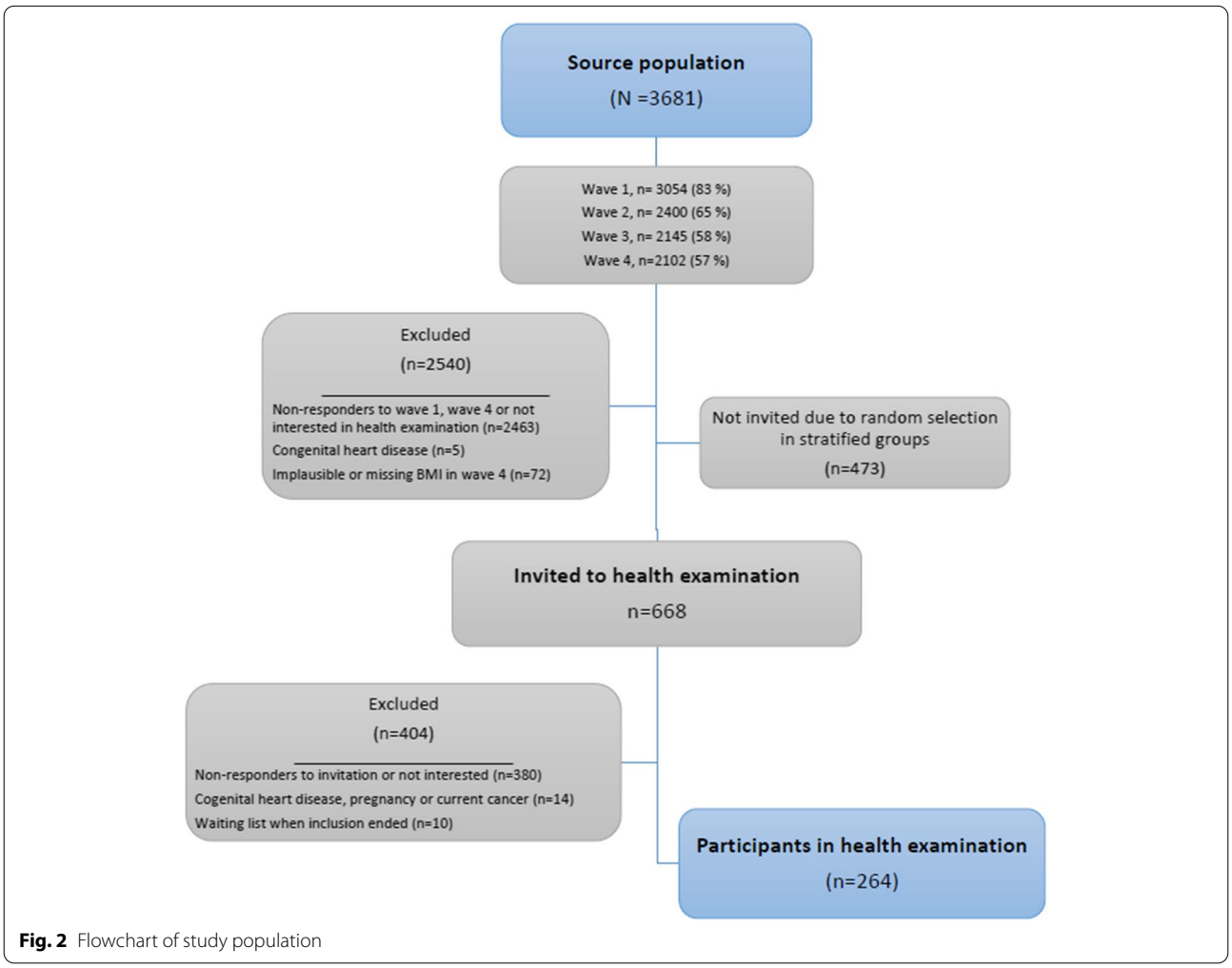

Fig. 2 Flowchart of study population

to supplement with parental disease history, birth weight and different indicators of SEP.

Assessment of socioeconomic position

Childhood SEP was evaluated by two different indicators; mother's highest level of education and household income, representing psychosocial and material resources, respectively. Data on mother's education was derived from educational registers and categorized into primary, secondary or tertiary education (≤10, 11–13 and > 13 years) at participant's ages 5, 10 and 14 years [26]. Household income was defined as annual equivalised disposable income, which is a weighted scale taking the size and distribution of family members into account. This data was derived from the Income Statistics Register provided by Statistics Denmark. We averaged the mean of each year when data was available for at least 3 years in each period at participant's ages 0–5, 6–10 and 11–15 years. We categorized the variable into low, medium and high household income at the 33.3rd and 66.6th percentiles of the entire West Jutland Cohort Study population.

Adult SEP was defined as participant's highest level of education at age 28 and categorized into primary, secondary or tertiary education (≤10, 11–13 and > 13 years) using data from educational registers [26].

SEP mobility was defined as upward, downward or immobile when adult SEP was above, below or the same as childhood SEP.

Definition of exposure

The latent effects model: SEP was assessed at age 0–5, 6–10 and 11–15 years, representing early childhood, middle childhood and late childhood as defined in previous research [22]. We evaluated all age-periods by both SEP-indicators knowing that high educational level of the mother in early childhood remains high in late childhood. However, the findings of the specific periods might be of relevance for comparison in future studies.

The pathway model: SEP was assessed at age 11–15 years and adult SEP at age 28 years. Lifestyle included physical activity and smoking status.

The cumulative model: SEP was assessed as a score summarizing the periods in the latent effects model and the participants own SEP at age 28 years. The score ranged from 0 to 8 where higher scores indicate greater exposure to low SEP. Results are presented as regression coefficients as well as categories of the level of exposure.

The social mobility model: Childhood SEP was assessed at age 11–15 years and adult SEP at age 28 years.

Assessment of cardiometabolic risk

The health examinations were performed from April 2018 to December 2019 [27]. Fasting blood samples were analysed at the central laboratory, Aarhus University Hospital and supplemented with Interleukin-6 analysed at BioXpedia (Aarhus, Denmark) using Meso Scale Diagnostics Technology V-plex human pro-inflammatory panel 1.

Definition of outcome

The biomarkers used to define cardiometabolic risk were defined a priori and represent markers of inflammation, hypertension, glucose metabolism and lipid status and included: High-sensitive CRP, interleukin-6, fibrinogen, systolic and diastolic blood pressure, insulin, glucose, high-density lipoprotein cholesterol and triglycerides. To include potential synergistic effects of different biological domains influencing disease risk, a continuous scale of cardiometabolic risk (CMR) was constructed. A continuous scale is statistically more sensitive and less prone to error compared to dichotomous data [28].

The nine cardiometabolic biomarkers used in the CMR score were standardized (inflammatory markers on the log-scale) to eliminate risk of unequal variance, and sample-weights, represented by latest self-reported BMI-group, were applied. The standardized scores were generated for each sex separately and summarized within each biological domain. The mean values of the four domains were then summarized and standardized to create CMR. Prior to standardization, we multiplied the values of high-density lipoprotein cholesterol by −1 to account for the inverse association with disease risk. Two participants with diabetes mellitus type 1 were excluded from the glucose metabolism domain but included in the overall CMR score.

Assessment of additional variables

Physical activity was derived from questionnaires at ages 15, 18, 21 and 28. For each age-point we dichotomised the variable according to the recommended level of physical activity for Danish adolescents (1 h/day) and adults (30 min/day), respectively [29]. If the participant was missing one response this was replaced with the mean value of the three available responses. The values across all years were summarized to a scale ranging from 0 to 4, where higher scores indicate higher levels of physical activity.

Smoking was categorized into current, former or never smoker at age 28–30 years.

Parental disease history was evaluated by the participants in a questionnaire received prior to the health examination. These data were supplemented with register data from the Danish National Patient Register on

cardiometabolic diagnoses from public hospitals. The diagnoses included diabetes mellitus, ischemic heart disease, acute myocardial infarction, atherosclerosis and stroke. The information was dichotomized into none or some if either of the parents had information on disease history. The variable was split into "parent with diabetes" and "parent with cardiovascular disease" depending on the specific diagnoses.

Birth weight was derived from the Danish Medical Birth Register that includes all national hospital- and homebirths [30]. It was categorized into high, normal and low (≥4500, 2500–4500 and < 2500 g) according to national guidelines.

Statistical analyses

All analyses were performed with STATA software version 16.0 (STATA corporation, College Station, Texas).

Initially, descriptive statistics were performed. The distribution of CMR, the four biological domains included in CMR, parental cardiometabolic disease history and lifestyle factors were presented by SEP categories in late childhood and young adulthood as mean (standard deviation) for continuous measures and number (percentage) for categorical measures. The correlation between educational level of the mother in late childhood and adulthood educational level was evaluated by Spearman's rank order correlation coefficient. Multiple linear regression models were fitted to estimate the association between childhood SEP and CMR by the latent effects, cumulative and pathway models as described in previous research [10]. We applied inverse probability-weights to the regression analyses to account for the sampling by BMI and sex. The models were checked by diagnostic plots of the residuals. We furthermore evaluated a potential effect measure modification of sex by including an interaction term in all models. As no significant interactions were found, all analyses were performed with both sexes together, adjusted for sex, birth weight and parental cardiometabolic disease history. When analysing social mobility, conventional linear regression models, including childhood SEP, adult SEP and mobility effects, cause potential problems due to multi-collinearity since the mobility per definition is measured by the difference between childhood and adult SEP. To take this into account we used diagonal reference models (DRM) to evaluate the distinct effects of social mobility on CMR, and further included birth weight, sex and parental disease history in the model. A detailed description of the equation used in DRM is to be found elsewhere [31]. However, DRM is specifically designed to disentangle social mobility in order to respect that outcome (measured by CMR) may be affected by both the origin (childhood SEP), destination (adult SEP) and the mobility itself [31, 32]. Furthermore, DRM estimates the relative weight of destination and origin. The measure is between 0 and 1. Hence a weight of 50% implies that origin and destination are equally important with regard to the outcome measure. Additionally, the four life course models were evaluated with respect to each of the biological domains included in the CMR score. The results concerning each distinct biological domain were presented in supplementary Tables S. 1–4.

Evaluating life course models

The latent effects model: The model suggests that latent effects from exposure to low SEP at specific periods in childhood remain, irrespective of later SEP. The model is supported if childhood SEP is inversely associated with CMR after adjustment for adult SEP at any of the three periods in childhood [10].

The pathway model: The model suggests indirect effects of childhood SEP through later experiences. The model is supported if childhood SEP is inversely associated with CMR prior to adjustment for lifestyle factors and adult SEP, and attenuated after this adjustment [10].

The social mobility model: The model suggests specific effects of either upward or downward social mobility. The model is supported if systematic differences remain in measures of CMR in social mobile individuals as compared to immobile individuals [31].

The cumulative model: The model suggests effects of the accumulation of exposure to low SEP throughout the life course. The model is supported if the indicators of SEP summarized throughout the life course are inversely associated with CMR [10]. The model is evaluated by a sum score of socioeconomic position in childhood (early, middle, late) and adulthood (age 28 years).

Results

Descriptive statistics are presented in Table 1. As illustrated, a total of 264 individuals (aged 28–30 years, 50% women) participated in the health examination. There were no statistical significant differences with regard to participant's lifestyle in the SEP-stratified groups. However, more from high childhood SEP were currently non-smokers and more often attained the recommended level of physical activity as compared to those from low SEP. The mean levels of CMR were higher in the groups with low childhood or adulthood SEP as compared to the groups with high SEP. Investigating the four biological domains separately, there was an inverse association between each domain and adult SEP, however, only the inflammatory domain was statistically significant inversely associated with childhood SEP, whereas the remainders showed minor differences across childhood SEP strata. Correlations between educational level of the

Table 1 Distribution of participants, cardiometabolic risk and additional variables by mother's and own educational level

	N	Mother's educational level, late childhood			N	Participant educational level, age 28		
		High	Average	Low		High	Average	Low
Total, participants	*259*	81 (31%)	115 (45%)	63 (24%)	*264*	164 (62%)	78 (30%)	22 (8%)
Men	*130*	50 (38%)	52 (40%)	28 (22%)	*132*	72 (54%)	47 (36%)	13 (10%)
Women	*129*	31 (24%)	63 (49%)	35 (27%)	*132*	92 (70%)	31 (23%)	9 (7%)
Current smoker		8 (10%)	21 (18%)	12 (19%)		16 (10%)	**22 (28%)***	5 (23%)
Physical activity (a)	*234*				*236*			
0–2		54 (71%)	78 (76%)	44 (80%)		113 (73%)	52 (79%)	12 (80%)
3–4		22 (29%)	25 (24%)	11 (20%)		42 (27%)	14 (21%)	3 (20%)
Parent with diabetes	*259*	9 (11%)	15 (13%)	**15 (24%)***	*264*	19 (12%)	**18 (23%)***	3 (14%)
Parent with cardiovascular disease	*259*	26 (32%)	28 (24%)	23 (37%)	*264*	46 (28%)	26 (33%)	6 (27%)
CMR (b)	*259*	0.1 (0.9)	0.1 (1.1)	**0.5 (0.9)***	*264*	0.0 (1.0)	**0.5 (1.0)****	**0.8 (1.2)****
Biological domains of CMR (b)								
Inflammation	259	0.1 (1.0)	0.1 (1.0)	**0.6 (1.0)****	264	0.1 (1.0)	**0.5 (1.0)***	0.5 (1.1)
Lipid status	259	0.1 (0.8)	0.1 (1.1)	0.4 (1.0)	264	0.0 (0.9)	**0.5 (0.9)****	**0.5 (1.5)***
Glucose metabolism	257	0.1 (1.0)	0.1 (1.2)	0.2 (0.9)	262	0.1 (1.0)	0.3 (1.2)	**0.6 (1.2)***
Hypertension	259	0.1 (1.0)	0.0 (1.0)	0.2 (0.8)	264	0.0 (0.9)	0.2 (0.9)	**0.7 (1.1)****

Abbreviations: *CMR* Cardiometabolic risk

Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures. *P*-values are conducted from ANOVA for continuous measures and Pearson's chi-squared test for categorical measures for questionnaire and clinical data. *$P < 0.05$ compared to "High" (bold text), **$P < 0.001$ compared to "High" (bold text)

[a] Number of questionnaire rounds with recommended level of physical activity

[b] Standardized values, with sample-weights applied

mother in late childhood and adulthood educational level were rather weak with a Spearman's rho of 0.22.

Life course models

Results from the adjusted analyses of mother's educational level and CMR evaluated by each of the four life course models are presented below and in Table 2. Crude estimates are presented in supplementary Table S. 5.

The latent effects model

Evaluating the association between childhood SEP and CMR by the latent effects model, no statistically significant differences between those growing up in families with high SEP and those growing up in families with average or low SEP were observed. However, there was a tendency towards increased levels of CMR among those in the low SEP stratum compared to those in the average or high SEP strata. The results were similar in early, middle and late childhood.

The pathway model

Evaluating the association between childhood SEP and CMR by the pathway model, we found statistically significant increased CMR among those growing up in families with low SEP compared to those with average or high SEP. The estimates were attenuated after adjustment for lifestyle and adult SEP, thus supporting the pathway model.

The social mobility model

Evaluating the association between intergenerational social mobility and CMR by DRM, we found the weight of destination to be greater than that of origin (74% vs. 26%, standard error 0.15).

We found no separate association with neither upwards or downwards mobility and CMR.

The cumulative model

Evaluating the association between accumulated exposure to low SEP and CMR, we found the greatest mean CMR among those with the greatest exposure to low SEP. This association remained statistically significant in the adjusted analysis.

Evaluating the association between household income and CMR, we found no associations in any of the adjusted life course models (Table 3).

Discussion

The main finding of this study was that children growing up in families with low SEP, measured by mother's highest level of education, are at greater risk of developing

Table 2 The association between mother's educational level and cardiometabolic risk in young adulthood evaluated by four life course models

	Adjusted cardiometabolic risk score (95% confidence interval)[a]			
	N	Mother's highest educational level		
		High	Average	Low
The latent effects model				
Early childhood	*246*	**Base level**	−0.2 (−0.5;0.1)	0.2 (−0.1;0.6)
Middle childhood	*246*	**Base level**	−0.2 (−0.5;0.1)	0.3 (−0.1;0.6)
Late childhood	*249*	**Base level**	−0.2 (−0.5;0.1)	0.3 (−0.1;0.6)
The pathway model				
Prior to adjustment for lifestyle and adult SEP	*249*	**Base level**	−0.1 (−0.4;0.2)	**0.4 (0.1;0.7)**
After adjustment for lifestyle and adult SEP	*227*	**Base level**	−0.2 (−0.5;0.1)	0.3 (−0.1;0.6)
The social mobility model	*249*			
Adult educational level: High		−0.1 (−0.9;0.7)	0.0 (−0.8;0.8)	0.0 (−0.8;0.9)
Adult educational level: Average		0.3 (−0.6;1.1)	0.3 (−0.5;1.1)	0.4 (−0.4;1.2)
Adult educational level: Low		0.7 (−0.2;1.5)	0.7 (−0.1;1.6)	0.8 (−0.1;1.8)
Separate upward mobility coefficient	−0.3 (−0.8;0.2)			
Separate downward mobility coefficient	−0.1 (−0.6;0.5)			
The cumulative model	*246*			
Regression coefficient	**0.1 (0.0;0.1)**			
0–2	**Base level**			
3–5	−0.1 (−0.4;0.2)			
6–8	**0.5 (0.1;0.8)**			

SEP Socioeconomic position

[a] Adjusted for sex, birth weight and parental cardiometabolic diseases

cardiometabolic diseases later in life, evaluated by a scale of cardiometabolic risk markers at ages 28–30 years. Concerning different life course models evaluating the association, we found support for the pathway and the cumulative life course models. Moreover, we found a statistically insignificant tendency towards increased cardiometabolic risk among those from low SEP evaluated by the latent effects model. This tendency was independent of the timing of the exposure in childhood. We found no separate association with intergenerational social mobility. However, we found basis for a protective effect of higher adult SEP, represented by educational attainment at age 28 years.

The current study is not the first to address the association between childhood SEP and later cardiometabolic risk by different life course models. Our findings are in line with former research showing that accumulated SEP across the life span is the best fitting life course model concerning adult health [9, 33]. However, most of the studies do not evaluate the pathway model. This was however evaluated by a study from the 1958 British Birth Cohort [34]. They found an inverse association between childhood SEP and allostatic load at age 44. They furthermore demonstrated that the most important indirect pathway was through participants own educational attainment followed by lifestyle factors.

Evaluating intergenerational social mobility, our study did not find a separate association with adult cardiometabolic health. However, we found the association with adult SEP to be greater than childhood SEP. These findings are in line with the acculturation thesis, stating that mobile individuals absorb their new surroundings and thus have greater impact from the destination than the origin [21]. A recent study by Savitsky et al. investigated social mobility by self-reported parental and adult occupation and education ($N=1132$) [35]. Outcome measures included anthropometry and traditional risk markers at age 32. The study pointed to adverse cardiometabolic outcome among downward and (mainly) upward mobile individuals. This was in contrast to the findings of the current study and displays the inconsistency within the social mobility literature. As opposed to the outcome measure of the current study Savitsky et al. did not include any markers of inflammation. Furthermore, the study used linear regression models to investigate the associations as opposed to the DRM used in the current study which might partly explain the different findings.

Some inconsistency does exist with regard to evaluating the association between childhood SEP and later

Table 3 The association between household income in childhood and cardiometabolic risk in young adulthood evaluated by four life course models

	N	Adjusted cardiometabolic risk score (95% confidence interval)[a]		
		Household income		
		High	Average	Low
The latent effects model				
Early childhood	*252*	**Base level**	−0.1 (−0.4;0.3)	0.0 (−0.3;0.3)
Middle childhood	*251*	**Base level**	−0.2 (−0.5;0.1)	−0.1 (−0.4;0.3)
Late childhood	*249*	**Base level**	0.1 (−0.2;0.4)	−0.1 (−0.5;0.2)
The pathway model				
Prior to adjustment for lifestyle and adult SEP	*249*	**Base level**	0.0 (−0.3;0.3)	−0.1 (−0.5;0.3)
After adjustment for lifestyle and adult SEP	*224*	**Base level**	0.0 (−0.3;0.3)	−0.3 (−0.7;0.1)
The social mobility model	*249*			
Adult educational level: High		0.0 (−0.9;0.8)	−0.1 (−0.9;0.7)	−0.1 (−0.9;0.7)
Adult educational level: Average		0.4 (−0.4;1.2)	0.4 (−0.4;1.2)	0.4 (−0.4;1.2)
Adult educational level: Low		0.8 (−0.2;1.7)	0.7 (−0.2;1.6)	0.7 (−0.2;1.6)
Separate upward mobility coefficient		−0.5 (−1.2;0.1)		
Separate downward mobility coefficient		−0.2 (−0.9;0.5)		
The cumulative model	*248*			
Regression coefficient		0.0 (0.0;0.1)		
0–2		**Base level**		
3–5		0.1 (−0.2;0.4)		
6–8		0.0 (−0.4;0.4)		

SEP Socioeconomic position

[a] Adjusted for sex, birth weight and parental cardiometabolic diseases

cardiometabolic diseases in a life course perspective. Some of this inconsistency rely on different interpretations of the life course, i.e. different life course models and different interpretations of each model, and furthermore the use of different SEP-indicators. For instance, one approach is to evaluate the association after adjustment for traditional confounders (e.g. smoking and physical activity), thus neglecting to see these factors as downstream effects of childhood SEP as suggested by the pathway model [9]. Evaluating the association between childhood SEP and cardiometabolic health by another SEP indicator, household income, we found no association regardless of the applied life course model. This is of interest as the two SEP indicators represent different aspects of SEP. The former representing psychosocial aspects and the latter material resources [8]. In contrast to the findings of the current study a very recent study by Najmal et al. investigated the association between family poverty (income) and traditional cardiometabolic risk markers in young adulthood ($N=1297$) [36]. They found statistically significant increased risk for women with family poverty as compared to those without. They found no association for men. The negative findings concerning income in the current study might be explained by the study context in a Danish welfare society with a high degree of social security. However, the link between educational level and cardiometabolic health remains largely unexplained. Is educational attainment protective due to better cognitive skills, greater knowledge and increased awareness about e.g. healthy lifestyle and public preventive strategies, also known as health literacy [37, 38]? Or is educational level also an indicator of other factors in childhood that influence both cardiometabolic health and educational attainment such as network, stress, parenting styles etc. [39]? Our descriptive results revealed increased inflammatory markers in those growing up in families with low SEP. Growing evidence suggests an association between various psychosocial stressors and low-grade inflammation [6, 40, 41]. This could indicate a potential link that needs attention in future research.

Strengths and limitations

Some limitations need to be addressed. Since this study is based on a sub-sample of a youth cohort, attrition and selection might bias the results. We applied probability weights in all regression-analyses and to the outcome measure to account for the sampling by sex

and BMI-group. Respondents to the questionnaires and participants in the health examination had higher SEP as compared to the source population [27, 42]. Unfortunately, it is not possible to know whether this selection was associated with cardiometabolic health and thus inducing differential selection bias. Previous research indicates that participation in studies is more likely with better health [43]. If this is the case in our study, the selection might have attenuated the results. The association between childhood SEP and cardiometabolic risk was investigated by a score of multiple biomarkers in a population of young adults prior to the development of manifest diseases. It is uncertain to what degree this score translates into clinical diseases. However, all biomarkers included in the score were known risk markers of cardiometabolic diseases and the approach has been used in a similar manner in previous studies [44–46]. Testing multiple life course models simultaneously might introduce the risk of false-positive conclusions (Type 1 error). Since all of the life course models were pre-established hypothesis we decided to avoid the risk of false-negative conclusions (Type 2 error) which could be introduced by applying a more restrictive approach of e.g. multiple hypothesis adjustment of the results [47]. However, adding Bonferroni correction did not change any of the overall conclusions.

The main strength of our study is the use of high quality registers in combination with longitudinal questionnaire information and a comprehensive panel of clinical biomarkers. This facilitated the empirical exploration of childhood SEP and cardiometabolic risk by all four life course models in addition to different SEP-indicators.

We used continuous scales of interrelated cardiometabolic risk markers rather than arbitrary cut-off values. This was done to respect the potential of synergistic effects of different biological domains influencing disease risk. Furthermore, investigating the impact of SEP prior to manifest diseases has the advantage of reducing potential epidemiological challenges due to bias from differences across SEP in relation to e.g. health care utility, healthcare provider bias and adherence to treatment [45]. Furthermore, some of the inconsistency in the social mobility literature might be explained by methodological and analytical challenges and the use of DRM is seen as a strength of this study [31].

Conclusion

In conclusion, this study strengthens the evidence for an overall association between the educational level of the mother and cardiometabolic risk in young adulthood. We found empirical support for the cumulative and pathway life course models. We found no specific timing across three different periods in childhood and no specific association with intergenerational social mobility. These findings emphasize the need to understand the underlying pathophysiological mechanisms as dynamic in nature and that improved cardiometabolic health can be gained throughout different developmental periods increasing the possibility for interventions. Improved understanding of the association with regard to health literacy, psychosocial stressors and dysregulated physiology is critical to inform policy makers and improve cardiometabolic prevention to support the continuing health of all children.

Abbreviations

BMI: Body Mass Index; CMR: Cardiometabolic Risk; DRM: Diagonal Reference Models; SEP: Socioeconomic Position.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-022-13158-0.

Additional file 1.

Acknowledgements

The authors want to thank all study participants and the study nurses, radiographers and secretaries at Cardiovascular Research Unit, Department of Cardiology and Department of Radiology, Regional Hospital West Jutland, Denmark.

Authors' contributions

All authors contributed to the design of the study. MKK analysed the data, prepared tables and figures and drafted the manuscript. All authors contributed to the interpretation of data, reviewed the manuscript and gave final approval.

Funding

The Karen Elise Jensen Foundation, Health Research Foundation of Central Denmark Region and the Research Foundation Gødstrup Hospital contributed to the funding of the study. None of the funding organizations had any influence on study design, analysis or interpretation of data.

Availability of data and materials

Restrictions apply to the availability of some or all data generated or analysed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Declarations

Ethics approval and consent to participate

The Danish Data Protection Agency and the National Committee on Health Research Ethics (no: 1–10–72-400-17) both approved the study. All participants signed a statement of informed consent prior to the health examination and the study complies with the Helsinki II Declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Received: 8 June 2021 Accepted: 30 March 2022
Published online: 09 April 2022

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Publisher's Note

Paper 3

Childhood socioeconomic position and cardiometabolic risk in young adulthood- the impact of mental health

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Short title:

Early psychosocial factors and cardiometabolic risk in young adulthood

Funding:

MKK received funding from The Karen Elise Jensen Foundation, Research Foundation of Central Denmark Region and Research Foundation Goedstrup Hospital

Disclaimers:

None declared

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Abstract

Background

Low socioeconomic position in childhood is associated with greater cardiometabolic disease risk later in life.

Objective

The aim of the current study is to examine the mediating impact of mental health on the association between childhood socioeconomic position and cardiometabolic disease risk in young adulthood.

Methods

We used a combination of national registers, longitudinal questionnaire-data and clinical measurements from a sub-sample (N=259) of a Danish youth cohort. Childhood socioeconomic position was indicated by the educational level of the mother and the father at age 14. Mental health was measured by four different symptom scales at four age-points (age 15, 18, 21 and 28), and combined into one global score. Cardiometabolic disease risk was measured by nine biomarkers at age 28-30 and combined into one global score by sample-specific z-scores. We conducted analyses within the causal inference framework and evaluated the associations using nested counterfactuals.

Findings

We found an inverse association between childhood socioeconomic position and cardiometabolic disease risk in young adulthood. The proportion of the association which was mediated by mental health was 10 (95 % CI: -4; 24) % and 12 (95 % CI: -4; 28) % using educational level of the mother and the father as indicator, respectively.

Conclusions

Accumulated poorer mental health in childhood, youth and early adulthood partially explained the association between low childhood socioeconomic position and increased cardiometabolic disease risk in young adulthood. These findings point to a potential for intervention in young age in order to impede the translation of childhood social stratification into later cardiometabolic disease risk disparities.

Keywords:

Social inequality, psychological factors, cardiometabolic diseases, young adults, epidemiology, causal inference

1. Introduction

There is a substantial social disparity in the prevalence of cardiometabolic diseases in most countries. Not only the present socioeconomic position (SEP) but also childhood SEP is associated with cardiometabolic disease risk in adulthood(1, 2). Multiple studies examine the association between childhood SEP and later cardiometabolic disease risk. However, the pathways through which differences in social stratification "gets under the skin" and translate into disparities in cardiometabolic disease risk is not entirely clear(3). Some of the association between childhood SEP and later cardiometabolic disease risk can be explained by differences in lifestyle and potential differences in the vulnerability to unhealthy lifestyle factors across SEP(4). Another possible explanation is the effect of mental health. Observational studies show that children growing up in families with lower SEP experience poorer mental health as compared to children growing up in families with higher SEP(5). Poor mental health is suggested to cause undesirable physiological effects in multiple biological domains

related to cardiometabolic disease risk, e.g. inflammation, lipids, blood pressure and glucose-metabolism and has become a recognised risk factors for cardiometabolic diseases(6, 7). Altogether, this proposes a mediating role of mental health in the association between childhood SEP and later cardiometabolic disease risk.

Different studies use different biomarkers and a variety of composite measures to assess cardiometabolic disease risk in association with social circumstances(8). The development of composite measures is consistent with growing evidence that pathological effects operate through an interplay of different physiological domains in an additive or synergistic manner. Common to all of the composite measures are the inclusion of multiple (patho)physiological domains often reflecting the cardiovascular system, metabolic system, inflammatory system and neuroendocrine system(8, 9). However, the included biomarkers and the construction of the different composite measures vary between studies(8-10). Improved understanding of the pathways and potentials to intervene upon the effects of lower childhood SEP on later cardiometabolic disease risk is critical to inform policy makers and improve prevention strategies to combat the increasing social disparity in cardiometabolic disease risk.

In the current study, we hypothesize that accumulated poor mental health *(*depressive symptoms, low sense of coherence, high perceived stress and poor self-esteem*)* in childhood, youth and early adulthood (age 15-28) mediates some of the association between childhood SEP and overall cardiometabolic disease risk at age 28-30.

2. Methods

2.1 Study population

This study included a sub-sample (n=259) of participants from the ongoing West Jutland Cohort Study(11). The cohort study comprised all individuals born in 1989 and living in a specific county in Western Denmark in 2004 (N=3,681)(12). All participants

were invited to fill in questionnaires regarding lifestyle, physical health and psychosocial factors at ages 15, 18, 21 and 28. Study participants were invited into the current study if they had responded to the initial and latest questionnaires and had indicated interest in a health examination. Invitations to be included in the health examination were based on sex and self-reported body mass index (BMI) (<25, 25-30, >30 kg/m2) at age 28 as described in detail previously(11). A flowchart illustrating the study population is presented in Figure 1.

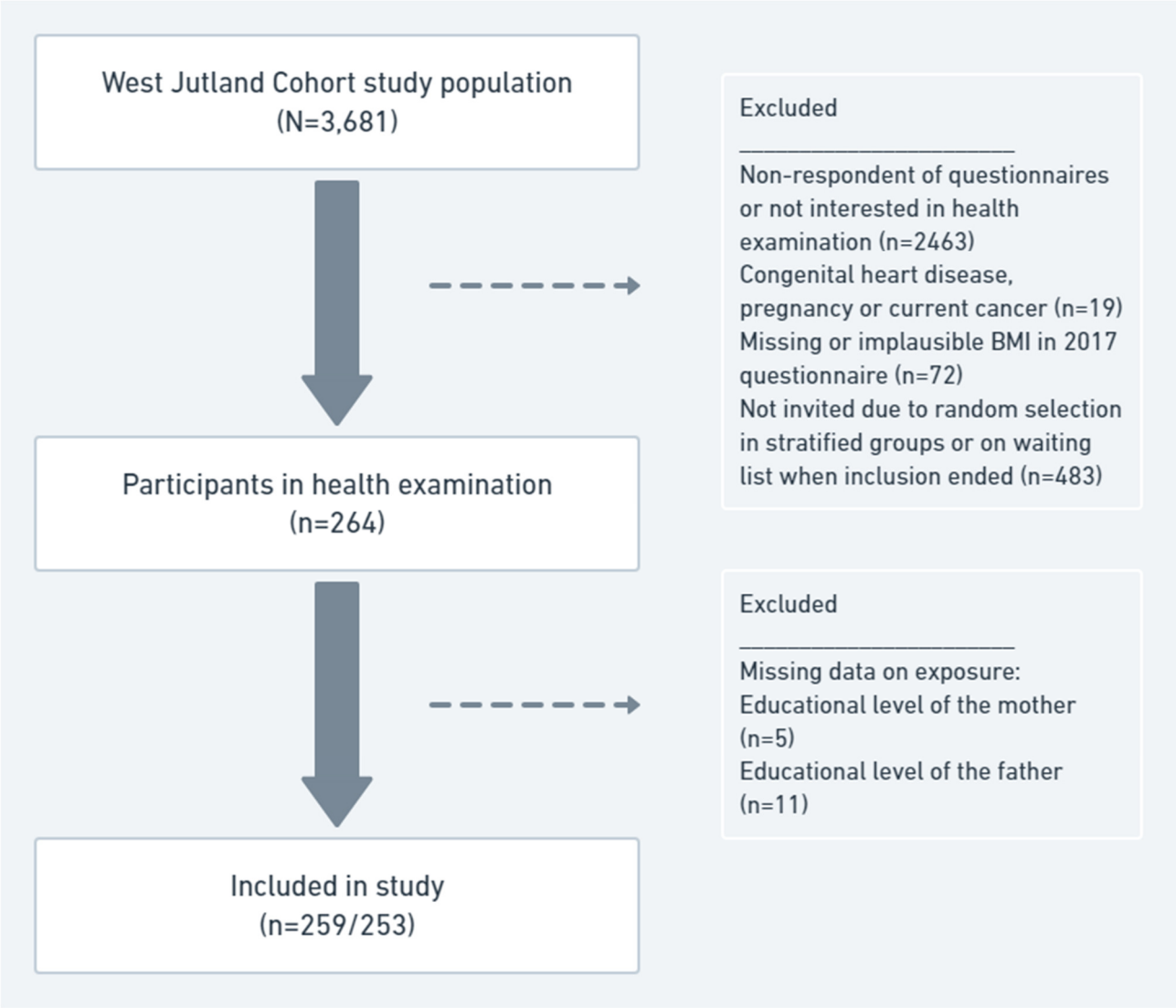

Figure 1. Flowchart of the study population

2.2 Causal structures

The study was conducted within the causal inference framework and analyses were guided by a directed acyclic graph (DAG) constructed based on knowledge about the assumed structures from the existing literature. A simplified DAG is presented below in Figure 2.

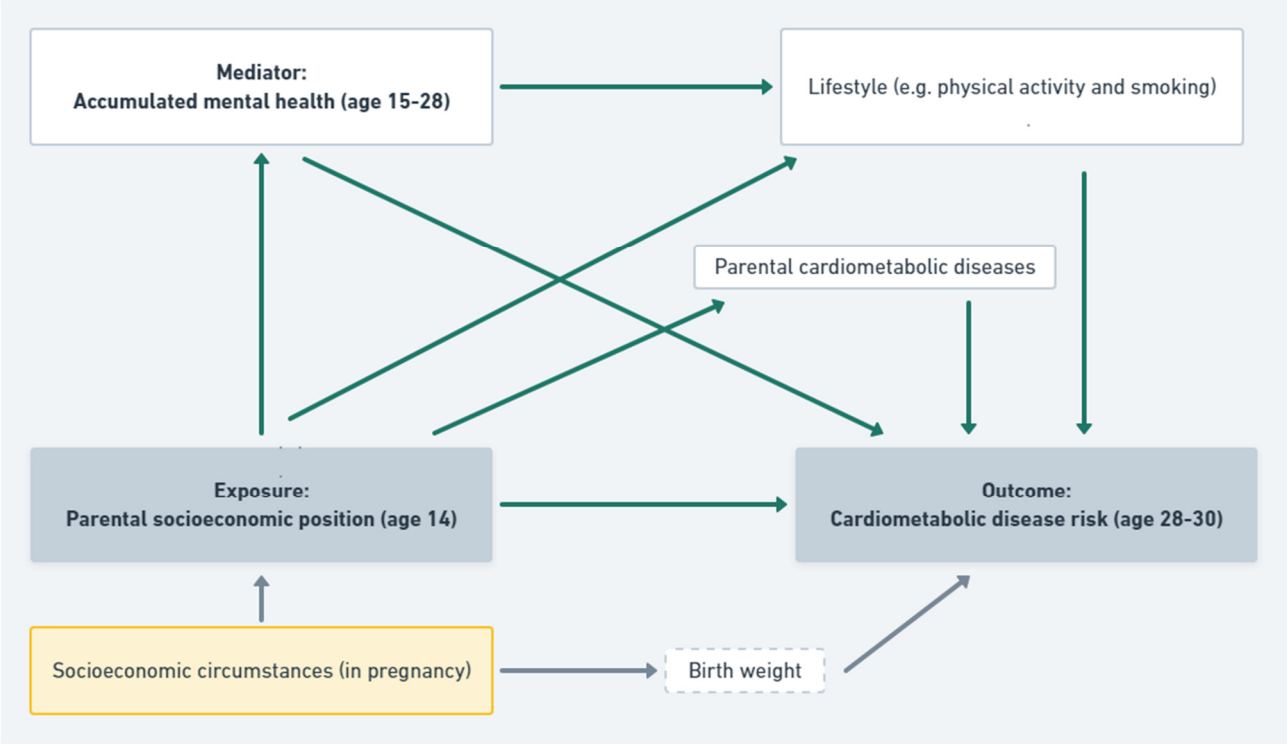

Figure 2. Directed acyclic graph of assumed structures

Using a DAG ensures a sufficient set of confounders to control for without introducing unwanted bias, e.g. collider bias, provided that the DAG correctly depicts the causal structures. Moreover, the DAG captures the overall associations and make sure not to control for intermediate variables on the path of interest and thus underestimate the effect by decomposing it into more parts. Below we will present the assessment of the

variables and some of the considerations underlying the nodes and arrows in the DAG. A particular focus will be on some of the usual confounders which are not included in the current study. Furthermore, details about response rates and the components of the mediator and outcome variables are shown in supplementary Table S.1-S.4.

2.3 Exposure

Based on a prior study from the same study population we decided to use parental educational level as indicator of childhood SEP(13). This indicator reflects psychosocial aspects of SEP rather than material aspects and appears to be the best indicator in a Danish welfare society(13, 14). The educational levels of the mother and father were investigated separately. Data included highest level of parental education when the participant was 14 years, and was derived from educational registers obtainable from Statistics Denmark and dichotomized into low (≤10 years) and high (>10 years)(15).

2.4 Outcome

All biological measures were obtained from a health examination when the participants were 28-30 years(11). The health examination was conducted by trained nurses using standardized operating procedures which are described in detail previously(11). Based on prior work, we created a continuous cardiometabolic risk (CMR) score from 9 biomarkers covering four different biological domains (inflammation, lipids, glucose-metabolism and blood pressure) in order to capture the overall cardiometabolic disease risk in young adulthood(10, 16). The biomarkers included in each domain are presented in supplementary Table S. 1. All biomarkers were standardized for each sex separately and inverse probability weights were applied to account for the sampling by BMI. We created a continuous score by

summarizing the mean values of the four domains. This overall score was then subsequently standardized. Higher scores indicate higher cardiometabolic disease risk.

2.5 Mediator

This study investigated the mediating impact of accumulated mental health (hereafter mental health) across childhood, youth and early adulthood rather than a single measure at a single age-point. We created a continuous, composite mental risk score by standardizing and summarizing four established symptom scales of the entire West Jutland Cohort Study population. Prior to this we conducted a factor-analysis and displayed the variation as a scree plot to support the use of one global score. All psychological factors were measured based on data from questionnaires across four age-points (age 15, 18, 21 and 28). Participants were included in the study if they had responded to at least two psychological measures at least two times. Higher scores indicated poorer mental health. The specific response rates concerning the psychological measures of study participants and the overall cohort population are presented in supplementary Table S. 2 and S. 3.

The psychological factors included in the score have previously been associated with SEP and cardiometabolic disease risk and comprise; sense of coherence, self-esteem, depressive symptoms and perceived stress(17). The first two factors are inversely related to the latter two and thus multiplied by -1 prior to summarizing them. Sense of coherence is believed to capture the ability of an individual to understand, manage and make sense of various life-situations in order to cope efficiently. In the current study we used a measure of meaningfulness evaluated by a revised 4-item short version of the original 29-item questionnaire proposed by Antonovsky(18). Self-esteem is defined as the individual's "*attitude of approval or disapproval toward*

oneself" and was measured by a 6-item short version of the original 10-item scale by Rosenberg(19). Depressive symptoms were measured by a 4-item short version of the Center for Epidemiological Studies Depression Scale for children, adolescents and young adults (CES-DC)(20). The scale is a general measure of psychopathology rather than a measure of depressive disorder. Perceived stress is the subjective measure of appraised stress by the individual. In the current study we used a Danish 4-item version of the original 14-item Perceived Stress Scale by Cohen(21). The specific items used in the questionnaires of the current study are presented in supplementary Table S. 4.

2.6 To be or not to be a confounder

Below we will summarize some of the considerations underlying the depiction of the structures presented in the DAG above.

Birth weight: As indicated in the DAG above (Figure 2), there is a backdoor through birth weight on the exposure-outcome path. Several studies find associations between low birth weight, acting as an indicator of poor conditions in utero, and increased cardiometabolic disease risk(22). Furthermore, epidemiological studies show that new-borns from lower SEP families have lower birth weight as compared to new-borns from higher SEP families(23). Based on the DAG above it is thus necessary to include birth weight as a confounder for the exposure-outcome relationship. Information about birth weight was derived from the Danish Medical Birth Register obtained at Statistics Denmark. However, due to approximately 4 % missing values in the register we supplemented the data with data from parental questionnaires when the child was 15 years old. Birth weight was used as a continuous measure.

Physical activity: Level of physical activity is related to cardiometabolic disease risk, childhood SEP and mental health. Individuals with better mental health are more likely to be physically active as compared to those with poorer mental health(24). However, most studies are cross-sectional and the direction and temporal nature of the relationship are thus difficult to determine(25, 26). Recently, Martins et al. published an updated systematic review of qualitative studies concerning adolescent perspectives on barriers and facilitators of physical activity(27). The authors describe individual (e.g. psychological factors) and social/relational factors as two of the major areas for barriers/facilitators for physical activity. Based on this knowledge we chose to grasp mental health as an antecedent of the level of physical activity. However, due to the uncertainty in the literature as to the direction of the association, we further conducted supplementary analyses including physical activity as a confounder of the mediator-outcome relationship. This analysis is presented in supplementary Figure S.1. Information about physical activity was derived from questionnaires at ages 15, 18, 21 and 28.

Parental cardiometabolic diseases: In addition to its association with SEP, cardiometabolic disease inheritance across generations are well established(28). However, manifest cardiometabolic diseases primarily occur in older age with a peak around age 55-74 for men and 65-84 for women(29). This means that parental cardiometabolic diseases primarily establish after parental attainment of educational level (exposure). Also, parental cardiometabolic diseases are not considered to affect mental health of their children in childhood and young adulthood (mediator) and are thus not included in the current study as a confounder.

Sex: Sex-differences in mental health (mediator) and cardiometabolic disease risk in early adulthood (outcome) are evident(30). To account for this the mediator and

outcome variables were standardized sex-stratified as described above. We further acknowledge the literature pointing towards potential moderating effects of sex in the exposure-mediator and exposure-outcome paths. Consequently, we inserted an interaction term between sex and SEP in all analyses.

2.7 Statistical analyses

All data were analysed with Stata software version 16.1 (Stata corporation, College Station, Texas). Initially, descriptive statistical analyses were conducted to present demographics, mental risk score and cardiometabolic risk score by exposure level. To make causal statements from observational data we used the counterfactual notation and G-computation to facilitate the possibility of comparing mean CMR score values under different scenarios as described in detail elsewhere(31). Since, in our DAG, the outcome (Y) is affected by the exposure (X) directly and through the mediator (M), the counterfactual outcome is a nested counterfactual Y(x,M(z)), which corresponds to the value of the outcome had the individual been exposed to x and had the mediator set to its value, M(z) under exposure z. The average total effect of SEP (exposure) on CMR (outcome) can be defined as the hypothetical contrast had everyone been exposed versus had no one been exposed. In this notation, the contrast corresponds to E(Y(1,M(1)))-E(Y(0,M(0))). The average total effect may then be decomposed into the pure direct effect, PDE=E(Y(1,M(0)))-E(Y(0,M(0))), and the total indirect effect, TIE=E(Y(1,M(1)))-E(Y(1,M(0))). The proportion mediated (PM) through mental health is thus defined as PM=TIE/(TIE+PDE) with TIE+PDE being the average total effect of SEP on CMR. The PM may be negative when TIE and TIE+PDE are in opposite directions, or positive when TIE and TIE+PDE are in the same direction. We fitted the models with variables as described above and further applied

inverse probability weights in all analyses to account for the sampling by sex and BMI. We applied bootstrapping with 100 replications to obtain valid confidence intervals.

3. Results

As depicted in Table 1, a total of 259 participants were included in the study. Individuals from families with lower SEP had increased mean levels of mental and cardiometabolic risk scores as compared to individuals from families with higher SEP. This is evident for the global scores of both mental risk and cardiometabolic risk and for all distinct domains included in the two risk scores.

Table 1. Descriptive statistics of socioeconomic position, mental health and cardiometabolic risk by parental educational level

	Educational level of the mother N=259		Educational level of the father N=253	
	Low	**High**	**Low**	**High**
Total, n (%)	63 (24)	196 (76)	74 (29)	179 (71)
Men	28 (22)	102 (78)	37 (29)	90 (71)
Women	35 (27)	94 (73)	37 (29)	89 (71)
Own Educational level, n (%)				
>13 years	31 (19)	130 (81)	36 (23)	121 (77)
11-13 years	25 (32)	52 (68)	25 (33)	50 (67)
≤10 years	7 (33)	14 (67)	13 (62)	8 (38)

Mental risk score *, mean (SD)	0.06 (0.52)	-0.03 (0.60)	0.06 (0.57)	-0.03 (0.59)
CES-DC *	0.06 (0.65)	-0.02 (0.71)	0.08 (0.76)	-0.02 (0.69)
Perceived Stress *	0.00 (0.68)	-0.08 (0.68)	0.04 (0.69)	-0.08 (0.67)
Sense of Coherence, inverse *	0.01 (0.56)	-0.01 (0.72)	0.05 (0.66)	-0.02 (0.67)
Self-esteem, inverse *	0.18 (0.71)	-0.03 (0.75)	0.07 (0.70)	0.00 (0.76)
Cardiometabolic risk score *, mean (SD)	0.51 (0.94)	0.12 (1.04)	0.52 (0.98)	0.11 (1.08)
Inflammation *	0.64 (1.04)	0.08 (0.96)	0.42 (0.97)	0.15 (1.04)
Lipid status *	0.37 (1.02)	0.07 (0.99)	0.40 (1.01)	0.06 (1.01)
Glucose metabolism *	0.25 (0.88)	0.13 (1.15)	0.37 (1.16)	0.10 (1.11)
Blood pressure *	0.16 (0.76)	0.04 (1.04)	0.25 (1.07)	-0.01 (0.94)

Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures. * Standardized values, with sample-weights applied. CES-DC, Center for Epidemiological Studies Depression Scale for children.

The results from the G-computation analyses are presented in Figure 3. The average total effects of childhood SEP on cardiometabolic risk are -0.52 (95 % CI: -0.83; -0.20) and -0.54 (95 % CI: -0.80; -0.28) using educational level of the mother and father as indicator, respectively. This corresponds to the hypothetical contrast was everyone growing up in families with low SEP versus was everyone growing up in families with high SEP. Decomposing these estimates, the pure direct effects, which are explained by other factors than mental health, are similar for the two indicator variables: -0.47 (-0.77; -0.16) and -0.47 (-0.75; -0.20). The total indirect effects,

explained by mental health, are -0.05 (-0.10;0.00) and -0.07 (-0.14;0.01), using educational level of the mother and the father, respectively. The proportion mediated by mental health is thus 10.03 (95 % CI: -4.03; 24.09) % and 12.20 (95 % CI: -4.25; 28.66) %, respectively.

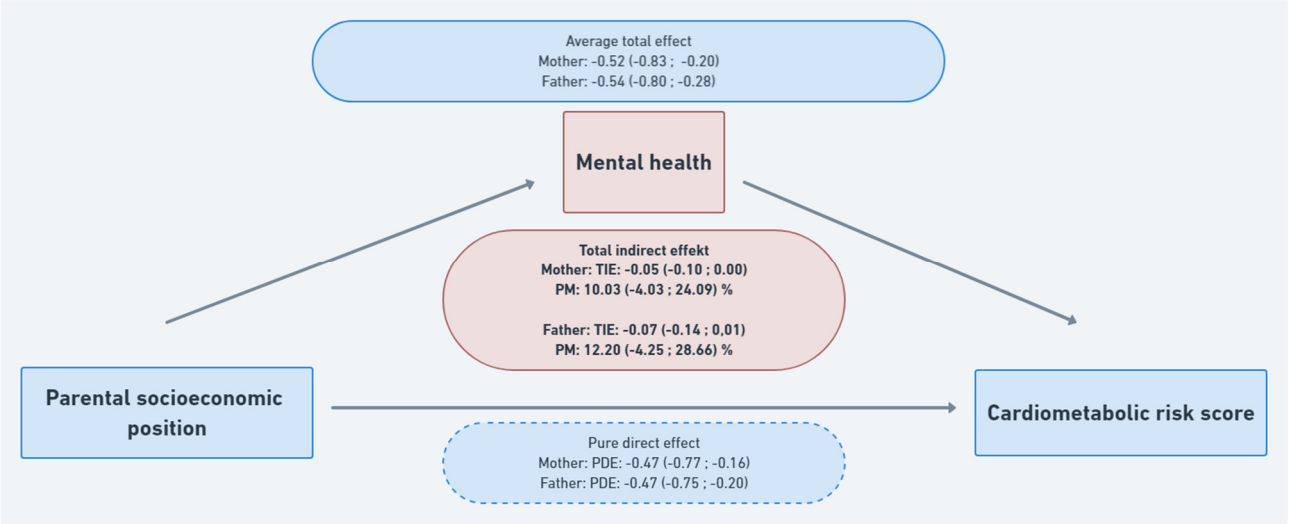

Figure 3. The mediating impact of mental health on the association between childhood socioeconomic position and cardiometabolic risk.

Figure legend: TIE, total indirect effect. PM, proportion mediated. PDE, pure direct effect. All estimates are presented with 95 % confidence intervals.

4. Discussion

In this study we examined the mediating impact of accumulated mental health in childhood, youth and early adulthood on the association between childhood SEP, indicated by parental educational level, and cardiometabolic disease risk at age 28-30. To investigate the association, we used G-computation and nested counterfactuals on longitudinal data. The primary results were that childhood SEP was inversely associated with cardiometabolic disease risk and that 10-12 % of the association could

be mediated through accumulated mental health. However, the estimates of the proportion mediated were fairly uncertain with confidence intervals ranging from inverse effect of mental health (-4 %) to 29 %.

A variety of elements might explain the robust association between childhood SEP and later cardiometabolic disease risk. Some of those are adverse health behaviours, less extracurricular activities, poor housing quality and environmental pollutants(32). These are all elements that accumulate in lower SEP environments. Recent literature further suggests psychosocial factors as mediators of the association(10, 33). However, empirical studies show mixed results. Doom et al. examined mediators between adolescent SEP and cardiovascular disease risk in young adulthood (M=28.9, 95 % CI = 26.6; 29.1 years) by path analyses on data from the National Longitudinal Study of Adolescent to Adult Health (N=14,493)(16). They found indirect paths through health behaviour and educational attainment but not through depressive symptoms. Some methodological aspects might challenge these findings. For instance, all mediators were measured simultaneously at one age-point and potential causal relationships between the mediators were not included, e.g. earlier depressive symptoms might be an ancestor of both educational attainment and health behaviour as previously described. Furthermore, the outcome measure was a Framingham based composite score including smoking status, which might be related to mental health through maladaptive coping mechanisms. Additionally, statistical challenges when analysing multiple mediators by path analyses might hinder firm conclusions about causality(34). In a study from the 1958 British Birth cohort (N=6,027) Winning et al. found that 37 % of the association between childhood social disadvantage and cardiometabolic risk at age 45 was mediated through childhood distress(10). These results are in line with our results however, the magnitude of the proportion mediated

is larger. This might partly be explained by differences in the exposure variables. Winning et al. created an index from 16 exposures related to family and socioeconomic hardship. This might strengthen the association with psychological distress and thus increase the proportion mediated.

There is no consensus about the best measure of mental health when examining the impact on the association between SEP and health outcomes(33). Recent research suggests an integrative approach concerning measures of mental health and recommends the use of composite scores to capture the overall and shared biological and behavioural effects(35). However, Ryff et al. recommend separate measures of mental well-being and mental ill-being as they might describe different aspects of mental health(36). To comply with this, we conducted supplementary analyses (not shown) for each psychological measure individually and for combinations of mental well-being (self-esteem and sense of coherence) and ill-being (perceived stress and depressive symptoms). All results were attenuated compared to using the global score which could indicate an increased robustness of the global score as compared to distinct measures in order to capture the overall mediating effect in the association. Conducting G-computation with a continuous mediator and outcome, VanderWeele et al. showed that non-differential measurement error of the mediator will bias the indirect effect towards the null and the direct effect away from the null(37). One can only speculate if adding further psychological measures to the global score could strengthen this measure even more and potentially increase the proportion mediated. The composite approach facilitates fusion of complex structures into overall mental health status. However, this approach requires complementary research in order to differentiate potential mediating effects of specific timing and specific mental health measures in the association. This remains important for future research.

Various mechanisms can plausibly explain the potential impact of mental health on the relationship between childhood SEP and cardiometabolic disease risk. Some of these are direct neurobiological modulations in childhood which can impact later health negatively through different pathophysiological mechanisms. This include structural changes in grey and white matter and altered metabolism of neurotransmitters involving serotonin, dopamine and glutamate(38). One of the other mechanisms relate to expected "acute" responses from the hypothalamus-pituitary-adrenal axis that can have prolonged impact when the negative feedback system is impaired due to persistent activation(39). Furthermore, acute and chronic psychosocial stress alter the autonomic nervous system with sympathetic predominance which further influences multiple biological domains related to cardiometabolic disease risk(40).

4.1 Strengths and limitations

Some notable strengths of the present study include multiple measures of mental health from multiple age-points, register based information on SEP and a robust measure of cardiometabolic disease risk respecting the potential additive/synergistic effect of various biological domains. In addition, both mediator and outcome were continuous measures instead of arbitrary cut-off values. Finally, using G-computation rather than traditional statistical approaches towards mediation analyses was seen as a strength in the current study context.

Our study has some limitations that need to be addressed. Most importantly, the study is based on a sub-sample of a cohort study and non-respondents and attrition might bias the results. Additional analyses, stratified by self-reported BMI- and sex, showed that overall questionnaire-responders have poorer mental health compared to the study-participants (supplementary Table S.5). In general, mental health is

364 inversely related to BMI. However, men with BMI >30 kg/m^2 participating in the study
365 have better mental health than men with BMI 25-30 kg/m^2. Since BMI is further
366 associated with cardiometabolic disease risk this selection might bias the total indirect
367 effect towards the null. However, running the G-computations without men with BMI
368 >30 kg/m^2 did not change the estimates noticeably (results not shown). A former
369 study investigating the initial non-participation in the West Jutland Cohort study finds
370 that individuals from lower SEP are more likely to be non-responders(12). If non-
371 responders also have increased cardiometabolic disease risk this might have
372 underestimated the total effect and thus overestimated the total indirect effect.
373 However, if non-responders furthermore have poorer mental health this might have
374 underestimated the total indirect effect pointing the proportion mediated towards the
375 results of the current study. Finally, the sample size was a limitation which might
376 explain the rather wide confidence intervals of the estimates.
377

378 ## 4.2 Conclusion

379 Our study finds that decreased mental health in childhood, youth and early adulthood
380 in part explains the association between lower childhood SEP and later
381 cardiometabolic disease risk. In addition to continued focus on childhood health
382 behaviours our findings emphasize the need to improve the overall mental health of
383 children growing up in families with lower SEP to decrease disparities in
384 cardiometabolic disease risk. In the meantime, further prospective studies including
385 multiple measures of mental health, larger study samples and suitable statistical
386 methods are needed to strengthen the current knowledge and clarify the magnitude of
387 the impact of mental health on the association between childhood SEP and
388 cardiometabolic disease risk.

Declarations

Acknowledgements:

The authors want to thank all study participants in the West Jutland Cohort Study and the study nurses and secretaries at the Cardiovascular Research Unit, Department of Cardiology, Regional Hospital West Jutland, Denmark.

Funding:

MKK received funding from The Karen Elise Jensen Foundation, Research Foundation of Central Denmark Region and Research Foundation Goedstrup Hospital.

Conflict of interest:

None declared

Authors' contributions:

MKK, TNW, JHA, MB contributed to the conception and design of the study and acquisition of data. MKK and SNH contributed to analysis. All authors contributed to interpretation of data. MKK drafted the article. All authors revised the article critically and gave final approval.

Ethical considerations:

The Danish Data Protection Agency and the National Committee on Health Research Ethics (no: 1-10-72-400-17) both approved the study. Participants signed a statement of informed consent prior to the health examination and the study complies with the Helsinki II Declaration.

Availability of data and materials:

Due to confidentiality restrictions apply to the availability of the data analysed during this study. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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Supporting information captions

Table S.1. Biomarkers included in the four biological domains of the outcome

Table S. 2. Number of study participants in health examination (N=264) who responded to each psychological variable in each wave

Table S. 3. Number of participants in the overall cohort (N=3,681) who responded to the psychological variables in each wave

Table S. 4. Items included in the psychological variables

Table S. 5. Mental risk score by self-reported Body Mass Index (BMI) at age 28

Supplementary Figure S. 1. Results of supplementary analyses when further adjusting for level of physical activity

Supplementary:

Table S.1. Biomarkers included in the four biological domains of the outcome

Biological domain	***Biomarkers***
Inflammation	High-sensitive CRP
	Interleukin-6
	Fibrinogen
Lipid status	Inverse High-density lipoprotein cholesterol
	Triglycerides
Glucose metabolism	Insulin
	Glucose
Blood pressure	Systolic blood pressure
	Diastolic blood pressure

Table S.2. Number of study participants in health examination (N=264) who responded to each psychological variable in each wave

Psychological variable, n (%)	**Wave 1** ***15* years**	**Wave 2** ***18* years**	**Wave 3** ***21 years***	**Wave 4** ***28 years***
Depressive symptoms	263 (99.6 %)	221 (83.7 %)	205 (77.7 %)	261 (98.9 %)
Sense of coherence	262 (99.2 %)	220 (83.3 %)	207 (78.4 %)	261 (98.9 %)
Perceived stress	262 (99.2 %)	219 (83.0 %)	210 (79.5 %)	264 (100 %)
Self-esteem	261 (98.9 %)	221 (83.7 %)	209 (79.2 %)	261 (98.9 %)

Table S.3 Number of participants in the overall cohort (N=3,681) who responded to the psychological variables in each wave

Number of responses to the four psychological variables, n (%)	**Wave 1** ***15*** **years**	**Wave 2** ***18*** **years**	**Wave 3** ***21 years***	**Wave 4** ***28 years***
0	628 (17.1 %)	1,286 (34.9 %)	1,680 (45.6 %)	1,714 (46.6 %)
1	6 (0.2 %)	11 (0.3 %)	5 (0.1 %)	61 (1.7 %)
2	30 (0.81 %)	9 (0.2 %)	27 (0.7 %)	12 (0.33 %)
3	139 (3.8 %)	98 (2.7 %)	111 (3.0 %)	74 (2.0 %)
4	2,878 (78.2 %)	2,277 (61.9 %)	1,858 (50.5 %)	1,820 (49.4 %)

Table S.4. Items included in the psychological variables

Mental health variable	**Items, wave 1**
Depressive symptoms	"During the past week, how much have you had the following feelings" (response categories: "not at all", "a little", "some" and "a lot") a) "I was happy this week" b) "I felt like kids I knew were not friendly or that they didn't want to be with me" c) "I felt sad" d) "It was hard to get started doing things this week"
Sense of coherence	1. How do you feel about the things you do every day? (response categories: "very interesting", "interesting", "OK", "boring" and "very boring") 2. About your daily life: (response categories: "very often", "often", "sometimes, "almost never" and "never") a) "How often do you do things that you think are meaningful?" b) "How often do you have the feeling that you don't really care about what goes on around you?" c) "How often do you have the feeling that there is little meaning in the things you do?"
Perceived stress	"In the last month, how often...?" (response categories: "very often", "fairly often", "sometimes", "almost never" and "never")

	a) "have you felt that you were unable to control the important things in your life" b) "have you felt confident about your ability to handle your personal problems" c) "have you felt that things were going your way?" d) "have you felt difficulties were piling up so high that you could not overcome them"
Self-esteem	"How much do you agree or disagree with the following statements? There are no right or wrong answers" (response categories: "strongly agree", "agree", "disagree", and "strongly disagree") a) "I feel that I have a number of good qualities" b) "I feel that I'm a person of worth at least equal to others" c) "I am able to do things as well as most other people" d) "I take a positive attitude toward myself" e) "On the whole, I am satisfied with myself" f) "All in all, I'm inclined to feel that I'm a failure"

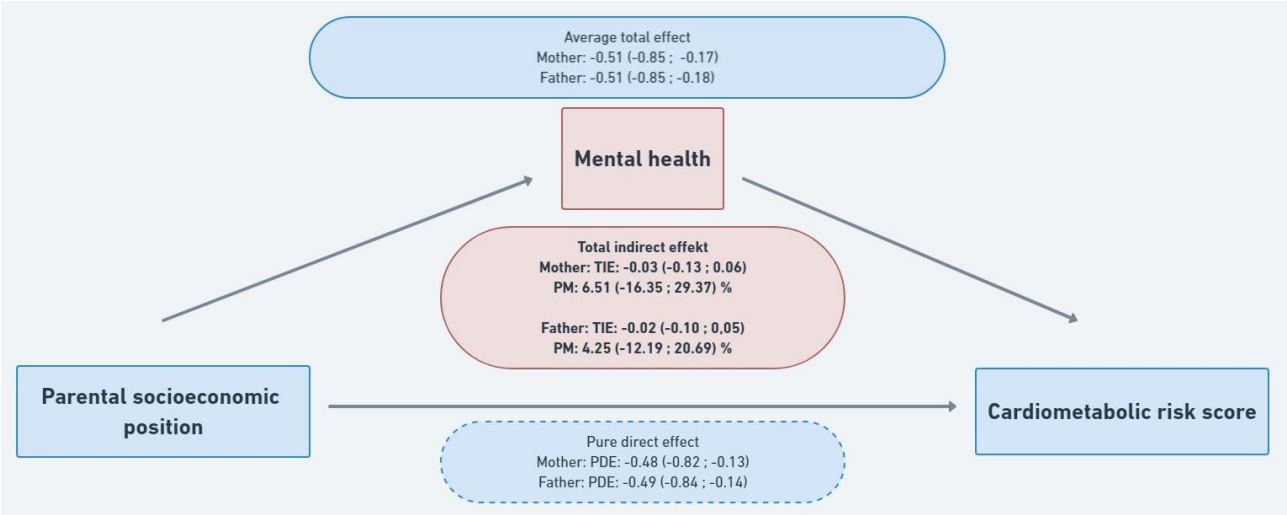
Legend: All questions and response categories were in Danish. The original questionnaires are available in Danish at www.vestliv.dk

Table S.5. Mental risk score by self-reported Body Mass Index (BMI) at age 28

	N	BMI<25 kg/m²	BMI 25-30 kg/m²	BMI>30 kg/m²
Participants	264	-0.16 (0.50)	0.02 (0.55)	0.14 (0.69)
Men	132	-0.16 (0.56	0.02 (0.54)	-0.03 (0.68)
Women	132	-0.16 (0.42)	0.02 (0.58)	0.28 (0.67)
All respondents	1819	-0.08 (0.58)	0.03 (0.62)	0.16 (0.68)
Men	753	-0.07 (0.60)	0.01 (0.59	0.06 (0.69)
Women	1066	-0.08 (0.57)	0.06 (0.65)	0.23 (0.67)

Data are presented as mean (SD). Higher score indicates poorer mental health.

Supplementary Figure S. 1 Results of supplementary analyses when further adjusting for level of physical activity.



Paper 4

Psychoneuroendocrinology 137 (2022) 105666

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Subjective social status and cardiometabolic risk markers in young adults

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ARTICLE INFO

Keywords:
Socioeconomic position
Social inequality
Composite cardiometabolic risk score
Epidemiology
Young adults
MacArthur scale

ABSTRACT

Background: Low subjective social status (SSS), the perceived status in the social hierarchy, is associated with cardiometabolic risk in middle-aged and older adults. However, most studies are cross-sectional and very little is known about the association in adolescence and young adulthood. The aims of this study were; a) to prospectively investigate the association between SSS at ages 15 and 28 and cardiometabolic risk at age 28–30 and b) to examine if such an association was independent of smoking, physical activity and objective measures of social position.

Methods: The study used questionnaire information at ages 15 and 28 from the West Jutland Cohort Study (N = 3681), health measurements from a sub-sample of the cohort (N = 264, age 28–30, 50% women) and information from population-based national registers. The independent variable was a measure of SSS evaluated by a 10-rung ladder scale and dichotomized at the 25th percentile of data from the cohort study population. The outcome measure was a composite score of cardiometabolic risk including measures of lipids, inflammation, blood pressure and glucose-metabolism. Co-variates included smoking, physical activity, childhood and adulthood socioeconomic position. Sex-stratified linear regression analyses were performed to evaluate the associations between SSS and cardiometabolic risk.

Results: In both sexes, low SSS at age 28, but not at age 15, was significantly associated with increased cardiometabolic risk at age 28–30. Neither smoking, physical activity, childhood or adulthood objective socioeconomic position fully explained the associations.

Conclusion: In young adulthood, SSS was inversely related to cardiometabolic risk after accounting for smoking, physical activity and objective measures of socioeconomic position. These findings suggest that SSS could play a role in the social disparities in cardiometabolic risk in addition to traditional measures of socioeconomic position.

1. Introduction

Social disparities in health are well-described across different countries and different diseases (Mackenbach et al., 2008; Adler and Rehkopf, 2008). Some of the most consistent and well-studied outcome measures include cardiometabolic risk markers and cardiometabolic diseases (Kaplan and Keil, 1993; Hostinar et al., 2017; Pollitt et al., 2005). Most of this research examines the effect of different indicators of objective socioeconomic position (SEP) such as income, occupation and educational attainment. However, within recent years, measures of perceived status in the social hierarchy, subjective social status (SSS), and the association with physical health have gained attention (Cundiff and Matthews, 2017).

Animal studies and experimental studies have underlined the importance of status perception in relation to cardiometabolic risk. A study by Pieritz et al. (2016) showed that experimentally manipulated low SSS induced imbalance in the autonomic nervous system represented by heart rate variability. The authors concluded that these findings support a causal role of social status in relation to cardiovascular disease. Furthermore, studies among nonhuman primates found social status differences concerning neurobiological functioning, depressive behaviour and coronary artery calcification (Shively and Day, 2015). In addition, analyses across different countries reveal that a higher degree of national income inequality is related to a higher prevalence of

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https://doi.org/10.1016/j.psyneuen.2022.105666
Received 1 November 2021; Received in revised form 3 January 2022; Accepted 7 January 2022
Available online 11 January 2022

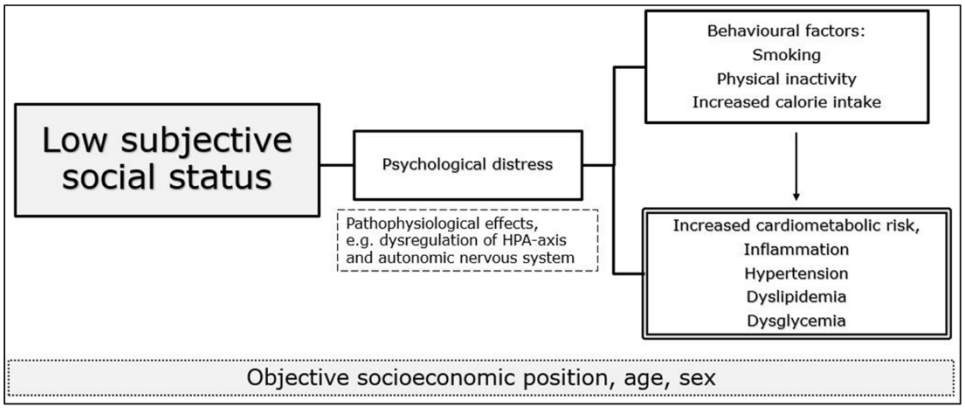

Fig. 1. Theoretical framework linking subjective social status with cardiometabolic risk.

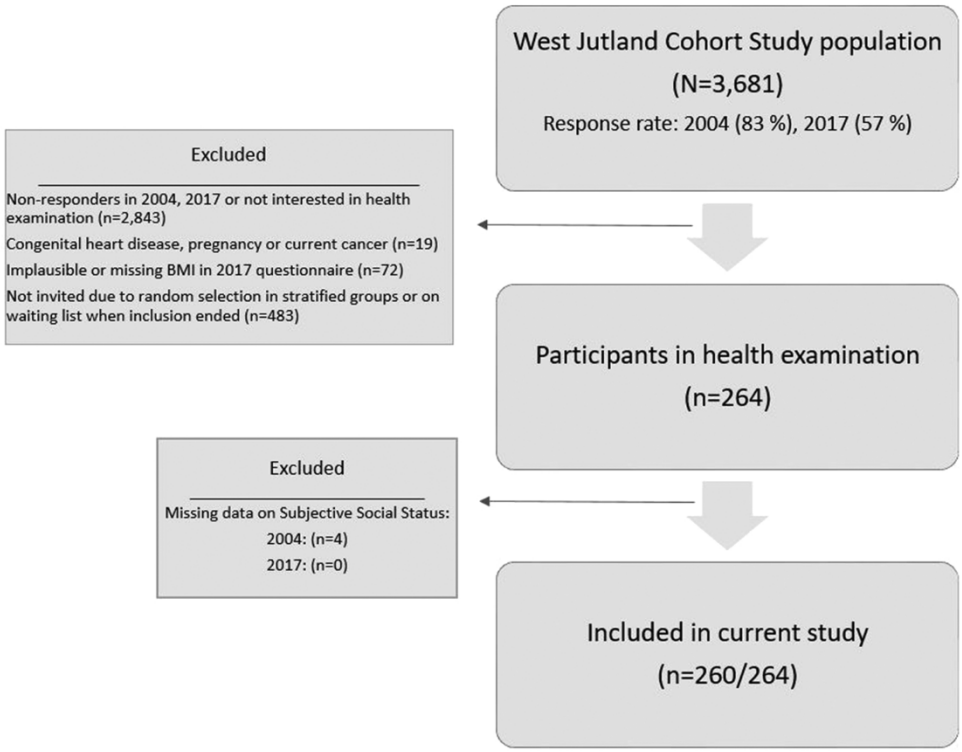

Fig. 2. Flowchart of the study population.

cardiometabolic risk factors, morbidity and mortality (Kim et al., 2008). Furthermore, populations with a higher income inequality report more status anxiety, e.g. the feeling of being looked down upon due to job situation or income, than populations with a lower income inequality (Layte and Whelan, 2014). Altogether, this indicates that status perception could provide unique information in order to better understand the social determinants of cardiometabolic risk and increase awareness of potential psychosocial factors influencing disease risk independent of income and education. Observational studies in this research area are sparse and most are cross-sectional and include individuals older than 50 years (Tang et al., 2016). Consequently, a recent meta-analysis by Cundiff et al. calls for prospective studies to evaluate social rank and measures of biology to explore the pathways to disease and thereby draw stronger causal inferences regarding the association between status perception and disease risk (Cundiff and Matthews, 2017). A meta-analysis by Tang et al. (2016) included nine studies and found that lower SSS was associated with significantly increased odds of various cardiometabolic outcomes (coronary artery disease, hypertension, diabetes and dyslipidaemia). All estimates were attenuated after inclusion of objective measures of SEP, however the trends remained consistent.

Various mechanisms have been hypothesized in order to explain the potential association between status perception and cardiometabolic diseases. Most focus has been on the relation between low status perception and psychological distress and further between psychological distress and cardiometabolic diseases (Everson-Rose and Lewis, 2005; Hoebel and Lampert, 2020). These studies indicate that psychological distress and its distal effects could act as an intermediate in the association. Plausible biological mechanisms involve different direct and indirect effects. Direct biological effects include dysfunctional regulation of the hypothalamic-pituitary-adrenal axis and sympathetic predominance of the autonomic nervous system (Everson-Rose and Lewis, 2005; Koban et al., 2021). Indirect effects include harmful coping mechanisms such as smoking, physical inactivity and increased calorie intake, which are all risk factors for cardiometabolic diseases (Cardel et al., 2016; Siqueira et al., 2000; Martins et al., 2021). Additionally, research

suggests a synergistic effect of various biological domains and recommends to incorporate multiple risk markers in the evaluation of early cardiometabolic risk (Huang et al., 2009; Hoogeveen et al., 2020). A simplified model of the potential pathways linking low SSS with cardiometabolic risk is illustrated in Fig. 1.

Previous studies from the West Jutland Cohort Study have found inverse associations between objective measures of childhood SEP and levels of cardiometabolic risk markers such as body mass index, lipids, blood pressure, glucose and low-grade inflammation in young adults ((Poulsen et al., 2018), MK. Kempel, TN. Winding, M. Böttcher, JH. Andersen, unpublished data). The primary aim of the current study was to examine if status perception, measured as SSS across two age-points; adolescence and young adulthood (age 15 and 28), was associated with a summary score of multiple cardiometabolic risk markers in young adulthood (age 28–30 years). Secondly, this study aimed to examine if the associations were independent of smoking, physical activity and objective measures of SEP in childhood and adulthood. We hypothesized that there would be an inverse association between SSS and cardiometabolic risk. We further hypothesized that this association would attenuate after inclusion of smoking, physical activity and objective measures of social position.

2. Methods

2.1. Design, study population and data sources

The current study was a prospective study using participants from a sub-sample (n = 264, 50% women) of the ongoing West Jutland Cohort Study (N = 3681). The aim of the cohort study was to investigate health inequities over the life course. Details about the recruitment process of the entire study population and the sub-sample have been described previously (Winding et al., 2014; Kempel et al., 2021). In brief, the West Jutland Cohort consists of all individuals born in 1989 and living in a specific county of Western Denmark when the study was initiated in 2004. All cohort members received a comprehensive questionnaire in 2004 (age 15) concerning various aspects of psychological, social and physical health. Round four of the cohort study was conducted in 2017 (age 28) and included an invitation to a clinical health examination to evaluate early risk markers of cardiometabolic diseases. Respondents who indicated interest in the health examination were randomly invited within six stratified groups based on sex and latest self-reported height and weight (body mass index <25, 25–30 and >30 kg/m^2) until a total of 264 participants were included. A flowchart of the study population and response rates in 2004 and 2017 are presented in Fig. 2. All questionnaire- and clinical data were linked with population-based register data on the research servers of Statistics Denmark using the civil registration number assigned to all Danish citizens (Laugesen et al., 2021). Below, the assessment of the variables included in the current study will be described. Furthermore, an overview of the description, categorization and data sources of each variable are offered in appendix, Table A1.

2.2. Exposure, subjective social status (SSS)

SSS was assessed using the MacArthur Scale of Subjective Social Status-Youth Version which is a pictorial 10-rung ladder asking the respondents to place themselves/their families on a ladder step based on perceived social status (Adler et al., 2000; Goodman et al., 2001). The scale ranged from 1 to 10 with higher values indicating higher perceived social status. Inspired by prior studies, we decided to categorize SSS to facilitate the interpretation of the results (Ferreira et al., 2018; McClain et al., 2021; Chen et al., 2012). Also, like in other studies some of the ladder scores included very few participants and the categorization thus facilitates more stable estimates (Hu et al., 2005). We choose to base the categorization on population-specific data in order to examine the impact of those perceiving themselves in the very bottom of the social hierarchy and the remaining participants in this specific society. As no consensus about thresholds was available, we dichotomized the scale into low and high based on the sex-stratified 25th percentiles of the entire West Jutland Cohort Study population. The dichotomization resulted in low SSS (ladder step 1–5) and high SSS (ladder step 6–10) for both sexes.

2.3. Outcome, cardiometabolic risk markers

Information about cardiometabolic risk markers was collected at a clinical health examination in 2018–2019 (age 28–30) by trained nurses using standardized operating procedures. The clinical health examination has been described in details previously (Kempel et al., 2021). Following the approach in previous studies investigating cardiometabolic risk in young age, we used multiple biomarkers obtained from fasting blood samples to create a continuous score of cardiometabolic risk (Winning et al., 2016; Non et al., 2014; Kamel et al., 2018). The nine biomarkers covered four biological domains; Inflammation (High-sensitive CRP, Interlukin-6 and Fibrinogen), lipids (Triglycerides and inverse values of High-density lipoprotein cholesterol), blood pressure (systolic and diastolic blood pressure) and glucose-metabolism (Glucose and Insulin). All nine biomarkers were standardized for each sex separately and sample-weights were applied to account for the sampling by body mass index. Initially, the mean value of each biological domain was calculated. Afterwards, a summary score of cardiometabolic risk (CMR) was created by standardizing the mean value of all four biological domains. Higher scores indicated higher cardiometabolic risk.

2.4. Covariates

We included childhood socioeconomic position (SEP), adulthood SEP, smoking and physical activity as co-variates in the analyses.

2.4.1. Socioeconomic position

Two indicators of childhood SEP were used; educational level of the mother and household income (Galobardes et al., 2006). Information about educational level of the mother (at age 14 of the participant) was obtained from Statistics Denmark using educational registers and categorized into high, middle and low (>13 years, 11–13 years and ≤10 years of completed school) (Jensen and Rasmussen, 2011). Information about household income was obtained from Statistics Denmark using the Income Statistics Register (Baadsgaard and Quitzau, 2011). Household income was defined as annual equivalised disposable income which is a weighted variable taking the size and distribution of the family into account. We used information across five years when the participant was 11–15 years old and calculated an average of the period if information for at least three years was available. Adulthood SEP was indicated by educational level of the participant at age 28 and was obtained from Statistics Denmark using educational registers and categorized into high, middle and low (>13 years, 11–13 years and ≤10 years of completed school) (Jensen and Rasmussen, 2011).

2.4.2. Health behaviour

Information about health behaviour included measures of physical activity and smoking status. Information about physical activity was obtained from questionnaires at ages 15 and 28. Physical activity was categorised into level 0–5 with higher levels indicating more physical activity each week (None, ½ hour, 1 h, 2–3 h, 4–6 h and ≥7 h). Information about smoking status was obtained from the questionnaire at age 15 and from a questionnaire at the clinical health examination at age 28–30. Smoking was dichotomized into ever (former/current) and never.

2.5. Statistical analyses

All analyses were conducted on the research servers of Statistics

Table 1
Descriptive statistics of participants by the level of subjective social status.

	Age 15						Age 28					
	Girls			Boys			Women			Men		
Subjective Social Status	n	Low	High	n	Low	High	n	Low	High	n	Low	High
Total, n (%)	131	18 (14)	113 (86)	129	21 (16)	108 (84)	132	21 (16)	111 (84)	132	25 (19)	107 (81)
Ladder score, Mean (SD)		4.6 (0.7)	7.1 (0.9)		4.2 (1.1)	7.2 (1.0)		4.2 (1.0)	7.2 (0.9)		4.3 (0.9)	7.3 (0.9)
Educational level of the mother, n (%)	128			127			129			130		
High		4 (22)	26 (24)		**6 (30)**	**43 (40)**		5 (24)	26 (24)		**4 (16)**	**46 (44)**
Middle		10 (56)	53 (48)		**4 (20)**	**47 (44)**		12 (57)	51 (47)		**11 (44)**	**41 (39)**
Low		4 (22)	31 (28)		**10 (50)**	**17 (16)**		4 (19)	31 (29)		**10 (40)**	**18 (17)**
Childhood household income Dkr, mean (SD)	127	**139,223 (36,207)**	**170,623 (37,623)**	129	147,212 (32,575)	177,327 (87,178)	128	156,401 (45,452)	167,757 (36,757)	132	166,853 (43,228)	173,706 (87,131)
Adult educational level, n (%)	131			129			132			132		
High		**8 (44)**	**83 (74)**		12 (57)	54 (58)		**8 (38)**	**84 (76)**		**9 (36)**	**63 (59)**
Middle		**7 (39)**	**24 (21)**		NA	40 (37)		**7 (33)**	**24 (22)**		**9 (36)**	**38 (36)**
Low		**3 (17)**	**6 (5)**		NA	10 (9)		**6 (29)**	**3 (3)**		**7 (28)**	**6 (5)**
Smoking, n (%)	131			129			132			132		
Never		13 (72)	96 (85)		NA	99 (92)		**10 (48)**	**83 (75)**		15 (60)	70 (65)
Ever		5 (28)	17 (15)		NA	9 (8)		**11 (52)**	**28 (25)**		10 (40)	37 (35)
Level of physical activity*, n (%)	130			129			130			126		
Low		NA	86 (77)		13 (62)	72 (67)		NA	81 (74)		13 (65)	68 (64)
High		NA	26 (23)		8 (38)	36 (33)		NA	29 (26)		7 (35)	38 (36)
Cardiometabolic risk score **, mean (SD)	131	0.7 (1.1)	0.3 (1.1)	129	0.2 (1.2)	0.2 (0.9)	132	**1.1 (1.3)**	**0.2 (1.0)**	132	**0.7 (1.2)**	**0.0 (0.9)**
Effect Size (Cardiometabolic risk score)***	0.36 (−0.14; 0.86)				0.00 (−0.47; 0.47)		0.86 (0.38; 1.33)				0.73 (0.28; 1.17)	

P < 0.05 comparing high with low are marked with bold text. P-values are from Pearson's chi-squared test and t-test for categorical and continuous measures, respectively.
* To ensure confidentiality of participants this variable is categorized based on recommended levels for adolescents (1 h/day) and adults (0.5 h/day), respectively in Table 1. **Standardized values, with sample-weights applied. *** Evaluated by Cohen's *d*.
NA, not available due to confidentiality of the participants.

Table 2
The association between subjective social status and cardiometabolic risk score in young adulthood.

	Age 15						Age 28					
	Girls			Boys			Women			Men		
	n	Low	High	n	Low	High	n	Low	High	n	Low	High
Model 1	131	0.3 (−0.2; 0.9)	Ref	129	0.0 (−0.6; 0,6)	Ref	132	**1.0 (0.3; 1.6)**	Ref	132	**0.6 (0.1; 1.2)**	Ref
Model 2	130	0.3 (−0.2; 0.8)	Ref	129	0.1 (−0.5; 0.6)	Ref	130	**0.9 (0.3; 1.6)**	Ref	126	0.6 (−0.1; 1.3)	Ref
Model 3a	127	0.3 (−0.2; 0.8)	Ref	127	-0.2 (−0.8; 0.4)	Ref	127	**1.1 (0.4; 1,8)**	Ref	124	0.7 (0.0; 1,4)	Ref
Model 4a	–	–	–	–	–	–	127	**0.9 (0.3; 1,6)**	Ref	124	0.6 (−0.1; 1,3)	Ref
Model 3b	126	0.3 (−0.3;0.8)	Ref	129	0.0 (−0.6; 0.6)	Ref	126	**0.8 (0.1; 1.4)**	Ref	126	0.6 (−0.1; 1,3)	Ref
Model 4b	–	–	–	–	–	–	126	**0.7 (0.0; 1,3)**	Ref	126	0.5 (−0.1;1.2)	Ref

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk).
Model 2: Model 1 + smoking and physical activity at age 15 and 28, respectively.
Model 3a: Model 2 + educational level of the mother.
Model 4a: Model 3a + adult educational level.
Model 3b: Model 2 + childhood household income.
Model 4b: Model 3b + adult educational level.
All estimates are presented with 95% confidence intervals. P < 0.05 *compared to "high"* are marked with bold text.

Denmark using Stata software version 16.1 (Stata corporation, College Station, Texas). Based on previous research in this area we conducted sex-stratified analyses (McClain et al., 2021). Initially, the correlation between the measures of SSS at age 15 and 28 of the entire cohort study population with available data was evaluated by Spearman's correlation. Afterwards, descriptive statistics of childhood SEP, adulthood SEP, health behaviour and cardiometabolic risk score, stratified on SSS at age 15 and 28, were presented. Values across strata were compared using Pearson's chi-squared for categorical variables and two sample t-test for continuous variables. Prior to analyses normality within each stratum was evaluated by visual plots. Cohen's *d* was used to describe the effect size by the standardized mean difference in cardiometabolic risk score across strata of SSS.

We performed hierarchical linear regression analyses to evaluate the associations between SSS and the cardiometabolic risk score. Model 1 was a simple linear regression estimating the association between SSS and CMR. Model 2 included physical activity and smoking status. Model 3 included physical activity, smoking status and childhood SEP. Model 4 (only exposure measure at age 28) included physical activity, smoking status, childhood SEP and adulthood SEP. All regression analyses were

weighted to account for the sampling probability in the six stratified groups (by sex and body mass index). The models were checked by post estimation plots of the residuals.

3. Results

Sex-stratified correlations of SSS measured at age 15 and age 28 were rather weak with a Spearman's rho of 0.20 for women and 0.19 for men. Descriptive statistics by exposure level are shown in Table 1. Male participants with higher childhood SEP, indicated by educational level of the mother, on average scored higher SSS at both age-points. Female participants with higher childhood SEP, indicated by household income, on average scored higher SSS at age 15. No differences in childhood SEP were seen among female participants comparing those with high and low SSS at age 28. There were positive associations between adult educational level and SSS among female participants at both age-points and among male participants at age 28. No significant differences in the level of physical activity were observed at any age-point across strata of SSS. However, female participants with low SSS at age 28 on average smoked more than female participants with high SSS. No differences in cardiometabolic risk score were observed across strata of SSS measured at age 15. However, at age 28, participants with low SSS on average had higher cardiometabolic risk scores compared to participants with high SSS with an estimated effect size of 0.86 (0.38; 1.33) and 0.73 (0.28; 1.17) for women and men, respectively.

Table 2 presents the results from the linear regression analyses. Statistical details about each model are presented in appendix Tables A2–A5. Regardless of sex, no statistically significant associations were observed between SSS measured at age 15 and the cardiometabolic risk scores. However, in girls, there was a tendency towards an inverse association between SSS and cardiometabolic risk. In both sexes, we found statistically significant inverse associations between SSS measured at age 28 and the cardiometabolic risk scores in the crude model 1. The associations were not affected by adjustment of smoking, physical activity and childhood SEP in model 2 and 3. A minor attenuation of the estimates was seen in model 4b among women when further adjusting for adult educational level. The estimates remained largely unaffected among men; however the confidence intervals became wider.

4. Discussion

In this study, we found that lower social status perception at age 28, but not age 15, was associated with increased cardiometabolic risk at age 28–30 in both sexes. The associations at age 28 remained largely unaffected when smoking, physical activity and childhood SEP was taken into account and was slightly attenuated after inclusion of objective measures of adulthood SEP.

These findings are consistent with previous studies reporting that status perception in adulthood is related to cardiometabolic risk independently of objective measures (Tang et al., 2016). The findings are further in line with results from the Jackson Heart Study ($N = 1724$, mean age 53.4 ($\pm$ 11.8)) reporting that the inverse association between status perception and metabolic syndrome severity was independent of lifestyle factors (Cardel et al., 2020). As opposed to this, a recent prospective study of a national sample of people $\geq$ 50 years from The English Longitudinal Study of Ageing ($N = 9972$) found that unhealthy behaviours to some extent explained the inverse association between status perception and cardiovascular mortality (Demakakos et al., 2018). The difference concerning adjustment by health behaviour might be explained by dissimilarities in the outcome measures, the age of the study participants and the fact that the English Longitudinal Study of Ageing also adjusted for body mass index. Conversely, in line with the current and other studies, the association was only slightly affected by adjustment for objective measures of SEP.

A number of studies suggest that individuals experiencing status inferiority might engage in activities to increase energy stores in order to cope with a potential future lack of resources (Cardel et al., 2016; Dhurandhar, 2016). This includes health behaviours to alter the energy balance toward a positive level. An experimental study supports this by showing that individuals placed lowest in the social hierarchy in a manipulated setting have increased calorie intake as compared to those placed highest in the hierarchy (Cardel et al., 2016). In the present study we do not have knowledge about the calorie intake of the participants. However, physical activity and smoking did not explain the overall association and focusing only on these traditional risk factors does therefore not seem sufficient. If increased calorie intake is a downstream effect of perceived low social status, this could be included in research analyses in order to better understand the indirect pathways from SSS to disease. Similarly, another explanation of the association is the status anxiety mentioned in the introduction. If the feeling of being looked down upon mediates the association this would be important knowledge for public health initiatives. The prevalence of cardiometabolic diseases is higher in countries with a higher degree of national income inequality (Kim et al., 2008). However, differences in cardiometabolic risk and all-cause mortality across objective measures of SEP are also apparent in rather egalitarian societies such as the Nordic countries with low relative income inequality measured by the Gini coefficient (OECD, 2021; Sundhedsstyrelsen, 2020; Mackenbach, 2017). In these countries absolute disparities in lack of material resources and food supply are minor and do not seem to sufficiently explain the total effects of SEP on health. Furthermore, a very recent review evaluated the association between income inequality and adult mental health (Tibber et al., 2021). The study finds that higher income inequality is associated with poorer mental health. Given these findings the observed association between SSS and cardiometabolic risk in a Danish welfare society might seem surprising. Since SSS is a relative measure, the social comparison underlying SSS could potentially be conceptualised differently in Denmark compared to countries with greater income inequality. The minor attenuation after inclusion of objective measures of SEP in the analyses of the current study suggest that status perception indeed contributes with other aspects of social position in relation to cardiometabolic risk. One explanation could be that status perception captures the individual level of social position initiating pathophysiological cascades rather than the somewhat general categorization of objectively measured SEP on the societal level. E.g. status perception might summarize the overall life circumstances relative to other people including multiple psychosocial factors such as occupation, educational level, social cohesion, self-esteem, and social network which are all correlated with health outcomes (Havranek et al., 2015). Singh-Manoux and colleagues from the British Whitehall II study suggest that SSS involves the "cognitive averaging of standard markers of socioeconomic position, while taking into account one's assessment of current and future prospects" (Singh-Manoux et al., 2003). This definition is supported by a recent study from the Brazilian Longitudinal Study of Adult Health which included 15,105 civil servants from six Brazilian states (Ferreira et al., 2018). The study showed that SSS in adulthood was a result of complex developmental processes including various family and individual indicators of SEP across the life course. This might also add to the explanation of the observed difference in the association between SSS and cardiometabolic risk across the two age-points in the current study. E.g. the measure at age 28 might be an accumulation of earlier experiences and thus a more robust indicator in relation to cardiometabolic risk compared to the measure at age 15. Another explanation could be the different grounds on which the individual base their perception in the social hierarchy at the two age-points. E.g. the period between age 15 and age 28 could be seen as a period of transition from mainly being influenced and dependent on parental environment in adolescence towards establishment of own family, profession, values and position in the society in young adulthood. Alternatively, overall difficulties in assessment of societal status perception at age 15 could induce bias towards the null due to random measurement error of the exposure (Weinberg et al., 1994). Additional analyses examining the association between status

perception in the school class rather than the society at age 15 in the current study, did not change the estimates substantially (results in appendix Tables A6 and A7). The rather low correlation between SSS measured at age 15 and age 28 further highlights that status perception is dynamic and thus potentially feasible for intervention. Additionally, as no strong long-term effects of SSS measured at age 15 were evident in the current study, it would be of interest for future studies to examine the changes in SSS over the life course and the association with cardiometabolic risk as well as the association between adolescent SSS and adolescent cardiometabolic risk.

Our study found stronger associations between SSS and cardiometabolic risk among young women as compared to men. This is in line with a recent study by McClain et al. (2021). The difference might be explained by both psychological and pathophysiological differences between the two sexes. First of all men and women might conceptualise SSS differently (Shaked et al., 2016). Secondly, the impact from low status perception and emotional distress might involve different downstream pathophysiological effects involving neurobiological sex-differences in the limbic system as well as sex-hormonal differences interacting with the HPA-axis (Killgore and Yurgelun-Todd, 2001; Pasquali, 2012). The current study underlines the importance of investigating the association sex-stratified and further attention towards understanding the sex-differences are warranted in future studies.

4.1. Strengths and limitations

Some limitations of the current study need to be acknowledged. The study population was an ethnically homogenous population with predominantly Caucasians. This does not allow for stratified groups evaluating non-Caucasians, which in other studies are found of great importance (McClain et al., 2021). Studies in multi-ethnic populations are warranted and researchers should ensure sufficient study-samples in order to explore how ethnicity influences the relationship between SSS and cardiometabolic risk. Another limitation of the current study was the possible effects of attrition and selection that lie in the nature of every cohort study. We were unable to fully account for all factors regarding non-responders which might have biased the results. A prior study from the West Jutland Cohort showed that non-respondents of the questionnaires were more likely to have parents from low SEP (Winding et al., 2014). We do not know if being non-respondent was also associated with SSS and cardiometabolic risk which could bias the results. Respondents of questionnaires often tend to be healthier than non-respondents (Greenberg et al., 2005). If being non-respondent was also associated with low SSS, this could have underestimated the estimates of the current study. Selection based on strata of sex and body mass index into the clinical health examination could also induce bias. However, the selection was conducted randomly within each stratum, and we accounted for the uneven distribution by applying sample-weights to the outcome measure and the regression analyses. Furthermore, supplementary analyses stratified by SSS and sex showed that the participants in the health examination did not differ significantly from other respondents of the questionnaires in 2004 and 2017 with regard to childhood SEP, adulthood SEP, smoking and physical activity (data not shown). We cannot exclude that the observed association between SSS and cardiometabolic risk is affected by reverse causation and prior studies have also emphasized the potential of common method bias, i.e. an underlying shared factor affecting both SSS and the health measure of interest (Singh-Manoux et al., 2005). However, the longitudinal study design with self-reported SSS at age 28 (2017) and the objectively measured cardiometabolic risk at age 28–30 (2018–2019) prior to manifest disease give some reassurance that the observed association is not merely due to reverse causation or common method bias.

Major strengths of the study included the prospective design, the use of high-quality national registers combined with questionnaire information comprising measures of SSS and health behaviour. Furthermore, the age-groups studied were seen as strengths due to the novelty within this area of research. Cardiometabolic diseases primarily occur in middle-aged and older populations. However, subclinical cardiovascular damage and metabolic abnormalities initiate in childhood and youth and track into older age (Zhang et al., 2019; Davis et al., 2001; Berenson, 2002). Given the modifiability of the cardiometabolic risk markers included in the CMR score, investigating the association in young age facilitates potentials for intervention with increased implication throughout the life course prior to manifest disease.

4.2. Conclusion

In conclusion, social status perception at age 28, but not age 15, was inversely associated with overall cardiometabolic risk in young adulthood in both sexes. Neither childhood SEP, adulthood SEP, smoking or physical activity fully explained the overall association. Perceived social status might be able to capture individual aspects of social position as compared to objective measures of SEP and thus provide valuable information within the area of health disparities. If the perception of status inferiority in itself increases cardiometabolic risk in young adulthood, interventions to reduce the effects, including the potential psychosocial consequences of this perception, are needed. Furthermore, social status perception might be easier to intervene upon in a societal setting as compared to objective measures of SEP. This may well include interventions to increase social network, trust and social participation. Furthermore, even though no strong association was found between SSS at age 15 and later cardiometabolic risk, improved focus in childhood could potentially impact status perception across the life course. This however, would need further clarification in future studies.

Ethical statement

The Danish Data Protection Agency and the Regional Committee on Health Research Ethics (no: 1-10-72-400-17) both approved the study. Participants signed a statement of consent prior to the health examination and the study complies with the Helsinki II Declaration.

Funding

This work was supported by The Karen Elise Jensen Foundation, Health Research Foundation of Central Denmark Region and the Research Foundation Goedstrup Hospital. None of the funding organizations had any influence on study design, analysis or interpretation of data.

CRediT authorship contribution statement

All authors contributed to the conception and design of the study and acquisition of data. All authors contributed to interpretation of data. MKK conducted the analysis and drafted the manuscript. All authors revised the article critically and gave final approval.

Acknowledgements

The authors want to thank all study participants in the West Jutland Cohort Study and the study nurses and secretaries at the Cardiovascular Research Unit, Department of Cardiology, Regional Hospital West Jutland, Denmark.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A

See Tables A1–A7.

Table A1
Overview of variables, categorization and data sources.

Variable	Description	Categorization	Source
Exposure, Subjective Social Status	The MacArthur Scale of subjective social status 10-rung pictorial ladder: 'Think of this ladder as representing where people stand in society. At the top of the ladder are the people who are the best off- those who have the most money, the most education, and the most respected jobs. At the bottom are the people who are the worst off- those who have the least money, least education, and the least respected jobs or no job. Mark your response on the ladder below that best represents where you think you/your family stand in relation to other families in Denmark". Dichotomized at the 25th percentiles based on the sex-stratified distribution of the entire cohort with available data.	Low High (ref)	Questionnaire at ages 15 and 28 years
Outcome	All biomarkers were obtained between April 2018 and December 2019. Fasting blood samples were drawn from an antecubital vein and stored at minus 80 degrees until analyses when inclusion ended.The mean values of each biological domain was used.	All biomarkers were standardized for each sex separately with mean= 0 and standard deviation= 1 and evaluated as continuous measures.	Health examination, age 28–30
Inflammation	Interleukin-6 High-sensitive CRP Fibrinogen	–	–
Lipids	Triglycerides Inverse values of High-density lipoprotein cholesterol	–	–
Blood pressure	Diastolic blood pressure Systolic blood pressure (Blood pressure was obtained with a regularly calibrated automatic device after five minutes of rest. Three consecutive measures were recorded and the mean values of the two last readings were used).	–	–
Glucose metabolism	Glucose Insulin	–	–
Cardiometabolic risk score	The mean value of the above mentioned biological domains (inflammation, lipids, blood pressure and glucose metabolism).	–	–
Covariates			
Sex	Biological sex	Girl Boy	The civil registry
Childhood SEP: 1. Educational attainment of the mother 2. Household income	1. Completed school of the mother (when the participant was 14 years old). Low: ≤ 10 years. Middle: 11–13 years. High:> 13 years. 2. Equivalised disposable household income when the participant was 11–15 years. Based on the OECD modified-scale: The first adult is assigned a weight of one, the subsequent adults > 14 years are assigned the weight of 0.5 and children 0.3. We calculated the average value of the period when data was available from at least three years.	Low Middle High	Statistics Denmark:1. Education registers 2. The income register
Adult SEP: Educational attainment of the participant, age 28	Completed school. Low: ≤ 10 years. Middle: ≥ 11–13 years. High:> 13 years.	Low Middle High	
Smoking status	"Do you smoke?"Age: 15:No, never No (but I used to) Yes (not every week) Yes (Not every day but every week) Yes (every day) Age 28–30:Yes No, never No (but I used to)	Never Ever (former/ current)	Questionnaire at age 15 and 28–30 years
Physical activity	"How many hours a week during leisure time do you usually exercise or play sports where you are out of breath or sweating?"Original categories: None, ½ hour, 1 h, 2–3 h, 4–6 h, and 7 h or more (at age 28: 7–10 h and 11 h or more).	Categories 0–5	Questionnaire at age 15 and 28 years

Table A2
The association between subjective social status and cardiometabolic risk score in young adulthood.

Girls, age 15								
Variable	*Model 1 (R^2=0.01)*		*Model 2 (R^2=0.09)*		*Model 3a (R^2=0.16)*		*Model 3b (R^2=0.10)*	
	β (SE)	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*
SSS								
High	Ref		Ref		Ref		Ref	
Low	0.3 (0.3)	0.202	0.3 (0.3)	0.301	0.3 (0.3)	0.243	0.3 (0.3)	0.360
Physical activity								
0			Ref		Ref		Ref	
1			-0.5 (0.6)	0.412	-0.4 (0.4)	0.334	-0.5 (0.6)	0.445
2			-1.2 (0.5)	0.019	-1.1 (0.3)	0.001	-1.0 (0.5)	0.050
3			-1.7 (0.5)	0.001	-1.4 (0.3)	0.000	-1.6 (0.5)	0.001
4			-1.2 (0.4)	0.007	-1.0 (0.3)	0.000	-1.2 (0.5)	0.011
5			-1.6 (0.5)	0.001	-1.5 (0.3)	0.000	-1.6 (0.5)	0.001
Smoking								
Never			Ref		Ref		Ref	
Ever			0.0 (0.2)	0.976	0.0 (0.1)	0.922	-0.1 (0.2)	0.587
Mothers education								
High					Ref			
Average					0.0 (0.2)	0.922		
Low					0.5 (0.2)	0.014		
Household income							0.0 (0.0)	0.779

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk).
Model 2: Model 1 + smoking and physical activity at age 15.
Model 3a: Model 2 + educational level of the mother.
Model 3b: Model 2 + childhood household income.
SE, Standard Error.

Table A3
The association between subjective social status and cardiometabolic risk score in young adulthood.

Boys, age 15								
Variable	*Model 1 (R^2=0.00)*		*Model 2 (R^2=0.06)*		*Model 3a (R^2=0.08)*		*Model 3b (R^2=0.07)*	
	β (SE)	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*
SSS								
High	Ref		Ref		Ref		Ref	
Low	0.0 (0.3)	0.982	0.1 (0.3)	0.851	-0.2 (0.3)	0.587	0.0 (0.3)	0.921
Physical activity								
0			Ref		Ref		Ref	
1			-2.2 (0.8)	0.006	-1.4 (0.3)	0.000	-2.2 (0.8)	0.007
2			-1.7 (0.8)	0.032	-1.0 (0.4)	0.005	-1.7 (0.8)	0.035
3			-1.9 (0.8)	0.012	-1.1 (0.2)	0.000	-1.9 (0.8)	0.015
4			-1.7 (0.8)	0.028	-0.9 (0.2)	0.000	-1.7 (0.8)	0.031
5			-2.0 (0.8)	0.009	-1.3 (0.2)	0.000	-1.9 (0.7)	0.011
Smoking								
Never			Ref		Ref		Ref	
Ever			-0.2 (0.4)	0.574	-0.1 (0.3)	0.839	-0.2 (0.4)	0.562
Mothers education								
High					Ref			
Average					-0.4 (0.2)	0.093		
Low					0.2 (0.3)	0.489		
Household income							0.0 (0.0)	0.129

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk).
Model 2: Model 1 + smoking and physical activity at age 15.
Model 3a: Model 2 + educational level of the mother.
Model 3b: Model 2 + childhood household income.
SE, Standard Error.

Table A4
The association between subjective social status and cardiometabolic risk score in young adulthood.

Women, age 28												
Variable	*Model 1 (R^2=0.08)*		*Model 2 (R^2=0.13)*		*Model 3a (R^2=0.19)*		*Model 4a (R^2=0.30)*		*Model 3b (R^2=0.14)*		*Model 4b (R^2=0.30)*	
	β (SE)	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*
SSS												
High	Ref		Ref		Ref		Ref		Ref		Ref	
Low	1.0 (0.3)	0.003	0.9 (0.3)	0.004	1.1 (0.3)	0.001	0.9 (0.3)	0.004	0.8 (0.3)	0.019	0.7 (0.3)	0.040
Physical activity												
0			Ref		Ref		Ref		Ref		Ref	
1			0.3 (0.4)	0.437	0.4 (0.4)	0.315	0.2 (0.4)	0.546	0.4 (0.4)	0.398	0.1 (0.4)	0.893
2			-0.4 (0.3)	0.287	-0.1 (0.4)	0.769	-0.4 (0.3)	0.259	-0.5 (0.4)	0.231	-0.8 (0.4)	0.063
3			-0.1 (0.3)	0.646	0.0 (0.3)	0.908	-0.2 (0.3)	0.490	-0.3 (0.4)	0.480	-0.5 (0.4)	0.191
4			-0.2 (0.3)	0.556	0.0 (0.4)	0.984	-0.1 (0.3)	0.684	-0.3 (0.4)	0.460	-0.5 (0.4)	0.273
5			-0.5 (0.4)	0.180	-0.3 (0.4)	0.507	-0.6 (0.4)	0.143	-0.6 (0.4)	0.150	-1.0 (0.5)	0.039
Smoking												
Never			Ref		Ref		Ref		Ref		Ref	
Ever			0.0	0.904	-0.2 (0.2)	0.384	-0.3 (0.2)	0.192	0.1 (0.2)	0.663	-0–1 (0.2)	0.539
Mothers education												
High					Ref		Ref					
Average					0.0 (0.2)	0.979	0.0 (0.2)	0.929				
Low					0.6 (0.2)	0.008	0.3 (0.2)	0.145				
Adult education												
High							Ref				Ref	
Average							0.9 (0.2)	0.000			1.1 (0.2)	0.000
Low							0.2 (0.3)	0.502			0.2 (0.3)	0.437
Household income									0.0 (0.0)	0.522	0.0 (0.0)	0.756

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk).
Model 2: Model 1 + smoking and physical activity at age 28.
Model 3a: Model 2 + educational level of the mother.
Model 4a: Model 3a + adult educational level.
Model 3b: Model 2 + childhood household income.
Model 4b: Model 3b + adult educational level.
SE, Standard Error.

Table A5
The association between subjective social status and cardiometabolic risk score in young adulthood.

Men, Age 28												
Variable	*Model 1 (R^2=0.06)*		*Model 2 (R^2=0.15)*		*Model 3a (R^2=0.18)*		*Model 4a (R^2=0.20)*		*Model 3b (R^2=0.15)*		*Model 4b (R^2=0.18)*	
	β (SE)	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*
SSS												
High	Ref		Ref		Ref		Ref		Ref		Ref	
Low	0.6 (0.3)	0.025	0.6 (0.3)	0.092	0.7 (0.4)	0.063	0.6 (0.4)	0.092	0.6 (0.3)	0.096	0.5 (0.3)	0.124
Physical activity												
0			Ref		Ref		Ref		Ref		Ref	
1			0.0 (0.4)	0.997	-0.2 (0.4)	0.512	-0.3 (0.4)	0.384	0.0 (0.4)	0.956	-0.2 (0.4)	0.621
2			-0.4 (0.3)	0.238	-0.3 (0.3)	0.332	-0.3 (0.3)	0.332	-0.4 (0.3)	0.226	-0.4(0.3)	0.254
3			-0.3 (0.3)	0.277	-0.3 (0.3)	0.301	-0.3 (0.3)	0.247	-0.3 (0.3)	0.283	-0.4 (0.3)	0.189
4			-0.5 (0.3)	0.154	-0.6 (0.3)	0.067	-0.6 (0.3)	0.059	-0.5 (0.3)	0.155	-0.5 (0.3)	0.128
5			-0.9 (0.3)	0.007	-0.9 (0.3)	0.013	-0.9 (0.3)	0.010	-0.9 (0.3)	0.006	-1.0 (0.3)	0.004
Smoking												
Never			Ref		Ref		Ref		Ref		Ref	
Ever			0.2 (0.2)	0.197	0.2 (0.2)	0.174	0.2 (0.2)	0.212	0.2 (0.2)	0.184	0.2 (0.2)	0.253
Mothers education												
High					Ref		Ref					
Average					-0.3 (0.2)	0.180	-0.4 (0.2)	0.095				
Low					0.0 (0.2)	0.907	-0.1 (0.2)	0.682				
Adult education												
High							Ref				Ref	
Average							0.1 (0.2)	0.610			0.0 (0.2)	0.969
Low							0.6 (0.4)	0.111			0.6 (0.4)	0.122
Household income									0.0 (0.1)	0.797	0.0 (0.0)	0.077

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk).
Model 2: Model 1 + smoking and physical activity at age 28.
Model 3a: Model 2 + educational level of the mother.
Model 4a: Model 3a + adult educational level.
Model 3b: Model 2 + childhood household income.
Model 4b: Model 3b + adult educational level.
SE, Standard Error.

Table A6
The association between subjective social status in school and cardiometabolic risk score in young adulthood.

Girls, age 15, school								
Variable	*Model 1 (R^2=0.02)*		*Model 2 (R^2=0.12)*		*Model 3a (R^2=0.18)*		*Model 3b (R^2=0.12)*	
	β (SE)	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*
SSS-school								
High	Ref		Ref		Ref		Ref	
Low	0.3 (0.2)	0.111	0.5 (0.2)	0.048	0.5 (0.2)	0.243	0.4 (0.2)	0.094
Physical activity								
0			Ref		Ref		Ref	
1			-0.5 (0.6)	0.411	-0.4 (0.4)	0.318	-0.4 (0.6)	0.469
2			-1.2 (0.5)	0.015	-1.1 (0.3)	0.000	-1.0 (0.5)	0.042
3			-1.8 (0.5)	0.000	-1.6 (0.3)	0.000	-1.7 (0.5)	0.000
4			-1.3 (0.4)	0.005	-1.1 (0.3)	0.000	-1.2 (0.5)	0.009
5			-1.7 (0.5)	0.001	-1.5 (0.3)	0.000	-1.6 (0.5)	0.001
Smoking								
Never			Ref		Ref		Ref	
Ever			0.2 (0.2)	0.512	0.2 (0.2)	0.506	0.0 (0.2)	0.899
Mothers education								
High					Ref			
Average					0.1 (0.2)	0.745		
Low					0.5 (0.2)	0.021		
Household income							0.0 (0.0)	0.535

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk).
Model 2: Model 1 + smoking and physical activity at age 15.
Model 3a: Model 2 + educational level of the mother.
Model 3b: Model 2 + childhood household income.
SE, Standard Error.

Table A7
The association between subjective social status in school and cardiometabolic risk score in young adulthood.

Boys, age 15, school								
Variable	*Model 1 (R^2=0.00)*		*Model 2 (R^2=0.06)*		*Model 3a (R^2=0.07)*		*Model 3b (R^2=0.07)*	
	β (SE)	*P*	*β (SE)*	*P*	*β (SE)*	*P*	*β (SE)*	*P*
SSS-school								
High	Ref		Ref		Ref		Ref	
Low	0.1 (0.3)	0.772	0.0 (0.3)	0.949	0.0 (0.3)	0.884	0.0 (0.3)	0.889
Physical activity								
0			Ref		Ref		Ref	
1			-2.2 (0.8)	0.006	-1.4 (0.3)	0.000	-2.2 (0.8)	0.006
2			-1.7 (0.8)	0.030	-1.0 (0.4)	0.015	-1.7 (0.8)	0.031
3			-1.9 (0.8)	0.012	-1.1 (0.3)	0.001	-1.9 (0.8)	0.013
4			-1.7 (0.8)	0.028	-0.9 (0.3)	0.009	-1.7 (0.7)	0.029
5			-2.0 (0.7)	0.007	-1.3 (0.3)	0.000	-1.9 (0.7)	0.008
Smoking								
Never			Ref		Ref		Ref	
Ever			-0.2 (0.4)	0.613	-0.1 (0.4)	0.823	-0.2 (0.4)	0.597
Mothers education								
High					Ref			
Average					-0.3 (0.2)	0.139		
Low					0.2 (0.2)	0.449		
Household income							0.0 (0.0)	0.129

Model 1: Crude estimates (higher values indicate higher cardiometabolic risk).
Model 2: Model 1 + smoking and physical activity at age 15.
Model 3a: Model 2 + educational level of the mother.
Model 3b: Model 2 + childhood household income.
SE, Standard Error.

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Mia Klinkvort Kempel

This declaration concerns the following article/manuscript:

Title:	Traditional and novel cardiometabolic risk markers across strata of body mass index in young adults
Authors:	M. K. Kempel, T. N. Winding, V. Lynggaard, S. Brantlov, J. H. Andersen and M. Böttcher

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Obes Sci Pract 2021 Vol. 7 Issue 6 Pages 727-737

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E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The study was designed in collaboration with my supervisors	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** Analyses were conducted by the PhD student and interpreted in collaboration with all co-authors	
Drafting the manuscript:	B
Free text description of PhD student's contribution ***(mandatory)*** The manuscript was drafted by the PhD student and revised after comments from all co-authors	
Submission process including revisions:	A

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The PhD student has essentially done all the work

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Title:	Evaluating the association between socioeconomic position and cardiometabolic risk markers in young adulthood by different life course models
Authors:	M. K. Kempel, T. N. Winding, M. Böttcher and J. H. Andersen

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D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The study was designed in collaboration with supervisors	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** Analyses were conducted by the PhD student and interpreted in collaboration with supervisors	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student drafted the manuscript and revised after comments from supervisors	
Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
The PhD student has essentially done all the work

Signatures of first- and last author, and main supervisor

Date	Name	Signature
12.04.22	Mia Klinkvort Kempel	Mia K Kempel
11/4 - 22	Johan Hviid Andersen	Johan Hviid Andersen
11/4 - 22	Johan Hviid Andersen	Johan Hviid Andersen

Date: 12.04.22

Mia K Kempel

Signature of the PhD student

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Mia Klinkvort Kempel

This declaration concerns the following article/manuscript:

Title:	Childhood socioeconomic position and cardiometabolic risk in young adulthood- the impact of mental health
Authors:	M. K. Kempel, T. N. Winding, M. Böttcher, S.N. Hansen and J. H. Andersen

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: PLOS ONE

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** The study was designed in collaboration with supervisors	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** Analyses were conducted by the PhD student and one of the co-authors. Data was interpreted in collaboration with all co-authors	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student drafted the manuscript and revised after comments from co-authors	
Submission process including revisions:	A

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Title:	Subjective social status and cardiometabolic risk markers in young adults
Authors:	M. K. Kempel, T. N. Winding, M. Böttcher and J. H. Andersen

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Psychoneuroendocrinology 2022 Vol. 137 Pages 105666

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

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