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Secular trends in cardiovascular risk factors among 38- and 50-year-old women based on the Prospective Population Study of Women in Gothenburg from 1968-69 to 2016-17

Degree Project in Medicine

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Abstract

Degree Project, Programme in Medicine

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Background: Cardiovascular diseases are the major cause of death in women worldwide. The key risk factors are highly preventable, including smoking, physical inactivity, high alcohol consumption, unhealthy diet, obesity, high blood glucose and diabetes, and elevated blood pressure, blood cholesterol and triglycerides.

Aims: To study secular trends in cardiovascular risk factors among middle-aged women in Western Sweden from 1968-69 to 2016-17 and adjust the most recent results between 2004-17 to socio-economic status.

Methods: The Population Study of Women in Gothenburg is a prospective observational study initiated in 1968. Representative samples of 38- and 50-year-old women (participation rate 58-91%, n=2488) were invited to a free health examination with physician interview, anthropometric measurements, and blood sampling every 12th year in 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17.

Results: Between 1968-2017, waist circumferences increased by 10cm in both ages reaching mean values 82 and 85 cm in 2016-17 in 38- and 50-year-olds, respectively. Plasma glucose levels increased over the whole period in both ages with highest increase between 2004-2017. High regular exercising increased, and inactivity decreased both between 1968-2017 and

2004-2017 but not equally in the lower socio-economic groups. Blood pressure and smoking decreased over the entire period, but these trends levelled off between 2004-2017.

Conclusion: There is a remaining concern of overweight and high blood glucose, and socio-economic differences in the improvements in physical activity. It is important to target health care actions and political decisions to decrease overweight and metabolic risk factors as well as to promote physical activity in all socio-economic groups.

Key words: cardiovascular diseases, women, secular trends, population study

Background

Introduction

Cardiovascular diseases (CVD), including diseases of the heart, vascular diseases of the brain and diseases in blood vessels, are the leading cause of death not only in men but also in women both worldwide, in Europe and in Sweden. (1-4) To describe the magnitude of the burden in Sweden, CVDs caused 14,184 deaths in Swedish women in 2019, responding for 32% of deaths in women, followed by cancers with 25%. (3, 5) Unfortunately, the earliest cardiovascular research programmes did not include women as coronary heart disease (CHD) was initially considered as a disease predominantly affecting men, but CVDs have later been shown to affect as many women as men. (1, 6) Since the early 1990s, more attention has been focused on women's cardiovascular health, but CVDs are still overall less studied in women than in men despite the equal burden. (6) There have been great changes in socio-cultural environment and women's status in Sweden between the 1960's and 2000's, from 70% of middle-aged women having only elementary school education and not working outside home to 90% of women having at least high school education and having income of their own. (7) In addition, women's physical health has improved but simultaneously, poor mental health and stress levels have increased. (8, 9) The relationships between environment and life-style-related cardiovascular risk factors are complex, and as the environment is continuously changing, there is even a continuous need for knowledge about risk factor levels in women population to be able to recognise and treat harmful changes in risk factor prevalence, in aim to decrease mortality and morbidity due to CVDs even in the future.

Pathophysiology of cardiovascular diseases

Ischaemic heart diseases (i.e. coronary heart disease/CHD) and cerebrovascular diseases (i.e. stroke) are the two major types of CVDs in both females and males, each causing over one third of cardiovascular deaths.(1) The pathophysiological process resulting in the majority of CVDs is known as atherosclerosis, a complex inflammatory process which, despite of broad research, is still not fully understood.(10) Atherosclerosis is a slowly developing process starting already in adolescence and early adulthood, but it remains usually asymptomatic during a long period until middle-age or older, when the symptoms of CVD generally manifest.(2) Atherosclerosis is considered to be a chronic inflammatory process enhanced by several preventable pro-atherosclerotic risk factors rather than just being a natural part of ageing, although family history (cardiovascular disease in a first-degree relative before the age of 55 years for men and 65 years for women) is an important risk factor.(1, 2, 10) The atherosclerotic process starts in sites near the branch points and inner curvature regions of artery walls where impaired laminar blood flow induces mechanical shear stress against the vessel lumen leading to a local inflammatory response in which low-density lipoprotein cholesterol particles (LDL) penetrate the damaged arterial walls and form deposits, so called plaques, in the vessel walls. LDL undergoes various modifications, among others oxidation, creating reactive oxygen species (ROS) which maintain and enhance the inflammatory process and plaque formation additionally.(10) Finally, the blood vessels become irregular and the lumen narrower, making it harder for blood to flow through the vessels and demanding oxygen transport to the affected organs causing ischaemic damages and eventually pain. Yet, the plaque can rupture, triggering the formation of a blood clot via activation of the

coagulation system, leading to a heart attack if it develops in the heart and stroke if it occurs in the brain.(1)

Cardiovascular risk factors

There is a strong scientific evidence for certain cardiovascular risk factors that play a central role in enhancing atherosclerosis.(1) The Northern Karelia Project is a historically significant project, demonstrating the power of population-based prevention through risk factor reduction via life-style changes. The project was initiated in the most eastern province of Finland in 1972 to reduce extremely high cardiovascular burden, as the local mortality in CHD was highest in the world there in that time. The community-based prevention program in Northern Karelia aimed to reduce serum cholesterol, blood pressure and smoking levels and resulted in a reduction of CHD mortality by 84% in the middle age population from 1972 to 2014 of which about 2/3 was explained by risk factor changes and 1/3 by improvements in medical treatments. (11)

Generally, cardiovascular risk factors can be classified into behavioural risk factors (incl. tobacco use, physical inactivity, unhealthy diet and harmful use of alcohol) and metabolic risk factors (incl. raised blood pressure (hypertension), raised blood sugar (diabetes and impaired glucose tolerance), raised blood lipids (hyperlipidaemia), and overweight/obesity).(1) In addition, socio economic factors such as poverty, low education and low level of employment have been associated with higher cardiovascular risk, mainly because of higher incidence of elevated blood pressure, total cholesterol, overweight and current smoking. (1, 6) Moreover, mental stress seems to be associated with increased CVD risk, in women especially before menopause.(12) Unfortunately, several cardiovascular risk factors often coexist in the same

individual and have an additive effect and therefore the total risk of developing CVD is determined by the combined effect of the cardiovascular risk factors.(2) In order to estimate the total individual risk profile, knowledge about the relationships between behavioural and metabolic risk factors, as well as about the levels of each unique risk factor, is needed to be able to target preventive life-style-, and pharmacological interventions.

Behavioural risk factors

Smoking is the most important preventable cardiovascular risk factor.(1) There is a clear dose-response relationship between the number of cigarettes smoked and the increased risk, but even low consumption (1-5 cigarettes a day) has a harmful effect.(2, 6) Smoking increases blood pressure, elevates the tendency of blood clot formation, promotes arterial inflammation in atherosclerosis and decreases the cardioprotective high-density lipoprotein cholesterol (HDL).(4, 6) Smoking cessation has shown to have a beneficial effect but the magnitude of the effect is unclear. Some studies suggest that ex-smokers are on the same cardiovascular risk level with never-smokers about 10 years after stopping smoking, others suggest that even longer time is required.(2)

Insufficient physical activity, defined by WHO as less than 5 times 30 minutes of moderate activity per week, or less than 3 times 20 minutes of vigorous activity per week, is a well-recognized cardiovascular risk factor. To describe the beneficial effects of physical activity, 150 minutes of moderate physical activity each week is estimated to reduce the risk of ischaemic heart disease by 30% and the risk of diabetes by 27%.(1) Physical activity has even a key role in weight control, improved blood pressure, lipid profile, insulin sensitivity and blood glucose control.(2)

High dietary intake of saturated fat, trans-fat cholesterol and salt are associated to cardiovascular risk whereas high intake of fruits and vegetables, fish, and replacement of saturated fats with polyunsaturated vegetable oils have shown to lower the risk of CHD. The amount of dietary salt consumed is an important determinant of blood pressure levels and overall cardiovascular risk (1, 2) In summary, a healthy diet can have beneficial effect to body weight control, desirable blood lipid levels and desirable blood pressure.(2) Unfortunately, it is difficult to measure epidemiological effects of dietary exposure so our knowledge considering beneficial and harmful nutrition is still limited.

The harmful use of alcohol is a risk factor for e.g. hypertension, acute myocardial infarction (heart attack), cardiomyopathy, cardiac arrhythmia and multiple other adverse health and social outcomes. The relationship between alcohol consumption and CVDs is complex and partly unknown. However, high alcohol consumption and binge-drinking (60 grams or more pure alcohol per day) have been associated with elevated risk of CVD. Overall, alcohol consumption is associated with multiple health risks that, clearly outweigh potential benefits.(2) Similarly with dietary factors, even the epidemiological effects of alcohol consumption are difficult to estimate.

Metabolic risk factors

Obesity is well recognized risk factor for cardiovascular diseases, and it is strongly associated to other major cardiovascular risk factors, including hypertension, insulin resistance, type II diabetes mellitus and hyperlipidaemia.(1, 13, 14) The increased cardiovascular risk is highly related to abdominal obesity and larger waist circumferences, whereas peripheral fat

deposition, measured i.e. by hip circumference, have been associated with relatively lower CVD risk.(15) To detect obesity in clinical practise, it is recommended to use both body mass index (BMI = weight (kg) divided by the square of height (m)) and waist circumference (WC) measurements, as they independently contribute to the prediction of obesity and thus complement each other, even though WC is considered to be better predictor than BMI in detecting abdominal adiposity. (14, 16-18) In a number of studies the waist-hip -ratio (WHR= waist circumference divided by hip circumference) has performed even better than WC in predicting CVD as it takes consideration to how the fat deposits are distributed in the body.(15) The goals for individuals should be to maintain a BMI in the range 18.5–24.9 kg/m², WC lower than 88cm (in women) and WHR lower than 0.8.(19) Obesity is defined by WHO as BMI ≥ 30 kg/m².(1)

Blood lipid profile includes low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglycerides (TG). Total cholesterol (TC) is a clinical measure of LDL, HDL and other lipid components together.(1) Hyperlipidaemia, meaning elevated levels of TC and LDL cholesterol, are closely related to obesity and metabolic abnormalities, and are major risk factors for heart disease and stroke.(6, 10) To describe the magnitude of the risk, one third of ischaemic heart disease is estimated to be related to high cholesterol and inversely, patients with high blood lipids are about twice as likely to develop CVD.(1, 10, 20) LDL cholesterol has a pro-atherosclerotic effect as it is deposited in the walls of arteries in the atherosclerosis, whereas HDL cholesterol protects against vascular disease by removing the “bad” LDL cholesterol out of the walls of arteries.(1) Thus, low levels of HDL correlate with higher risk of CVDs which has suggested to be even more predictive for heart disease in women compared to men.(21) High TG levels are often seen

together with low HDL levels and this combination has been associated with increased CHD risk, again to a greater extent in women than in men.(6) WHO defines risk levels for blood lipids as TC \geq 5.0 mmol/l, LDL \geq 3.0, HDL<1.3 mmol/l in females (<1.0 mmol/l in males), and TG <2.0 mmol/l. For individuals with established CVD or diabetes even lower target values, TC<4.0 and LDL<2.0, are recommended.(2)

Raised blood pressure (hypertension) is a major risk factor for coronary heart disease and, especially to vascular diseases of the brain, as undetected and uncontrolled hypertension is a major contributor to stroke worldwide.(1, 4) WHO recommends blood pressure less than 140/90mmHg (Systolic blood pressure (SBP)/diastolic blood pressure (DBP)) in order to lower cardiovascular risk but even lower levels (<130/80 mmHg) are recommended for those with established cardiovascular diseases or diabetes.(2) The cardiovascular risk due to hypertension can be reduced through non-pharmacological methods, including non-smoking, lower dietary salt intake, physical activity, limiting alcohol intake and maintaining normal body weight, as well as through pharmacological treatments.(2, 22)

Diabetes (commonly type 2) is a strong cardiovascular risk factor as up to 75-80% of diabetic patients die of CVDs and women with diabetes have estimated to have up to seven-fold increased risk for cardiovascular events compared to non-diabetic women.(6) Type-2 diabetes, is characterized by dysregulated glucose balance in the body, mainly due to cellular insulin resistance which leads to increased blood glucose levels.(23) Normal fasting plasma glucose is a level of <5.6 mmol/l, and diabetes is defined as fasting plasma glucose >7.0 mmol/l. The fasting plasma glucose between 6.1—7.0 mmol/l indicates for impaired fasting glycaemia (IFG) which also increases the risk for future development of diabetes and

CVDs.(1, 24) Obesity is the most critical factor in development of diabetes and other metabolic disorders, including hypertension and hyperlipidaemia, and these tend to exist together in the same individuals, referred as metabolic syndrome.(23) Thus, lifestyle-interventions and diet control play key roles in treatment of diabetes but that do not always give a satisfactory effect. WHO recommends medical treatment with metformin for individuals with persistent fasting blood glucose > 6 mmol/l.(2)

Secular trends in cardiovascular risk factors

The concept 'secular trends' is used to describe the development in risk factor prevalence over time in same-aged and same-sex population cohorts. Knowledge about secular trends in cardiovascular risk factors is essential to be able to target health promotion acts and to follow-up the results from earlier interventions in aim to decrease cardiovascular mortality and morbidity. Decreasing trends in several cardiovascular risk factors such as smoking, alcohol consumption and blood cholesterol have been observed and CVD mortality have decreased overall in Europe during the past decades, but the burden of CVDs is still significant in women as well as men.(4) While beneficial trends in certain risk factors have been observed, there is now a rising concern about the increasing prevalence of metabolic risk factors, particularly overweight/obesity and diabetes.(4) To our knowledge, there are only few populational long-term studies including women. Thus, The Population Study of Women in Gothenburg (PSWG) is a unique cohort study as it was initiated already in 1968 and is still ongoing, extending over five decades.(25) This study uses data from PSWG to describe secular trends in cardiovascular risk factors among middle-aged women from 1968-69 to 2016-17.

Aim

The aim of this study was to continue the documentation of short- and long-term secular trends in cardiovascular risk factors among 38- and 50-year-old Swedish women by using data from Prospective Population Study of Women in Gothenburg (PSWG) from 1968-69 to 2016-17. The risk factors included in this study were body weight and height, body mass index (BMI), waist and hip circumferences (WC, HC), waist-hip ratio (WHR), systolic and diastolic blood pressure (SBP, DBP), hypertension diagnosis, antihypertensive treatment, s-cholesterol, s-triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), p-glucose, self-reported diabetes, usage of tobacco products, alcohol consumption, and leisure time physical activity. The primary objective was to describe trends in development of the predetermined cardiovascular risk factors in different cohort years over the whole study period 1968-2017 and between the two most recent examinations 2004-2017, respectively, in aim to analyse both long-term- and the latest changes in risk factor trends among Swedish middle-aged women. The secondary objective was to adjust the results for socio-economic status (SES) to study possible socio-economic gaps with especial focus on the two latest examinations.

Material and methods

Population and Data collection

The Prospective Population Study of Women in Gothenburg (PSWG) was initiated in 1968 with health examinations of representative samples of different age-cohorts of women living

in Gothenburg. Follow-up examinations of 38- and 50-year-old women were conducted in 1980-81, 1992-93, 2004-05 and 2016-17, and new individuals in respective ages were continuously recruited to assembly data for cross-sectional comparisons. This study is based on cross-sectional data from 38- (n=1091) and 50-year-old (n=1397) women who participated in PSWG in years 1968-68, 1980-81, 1992-93, 2004-05 and 2016-17. The number of participants and participation rates in respective examination years are illustrated in figure 1. Unfortunately, fewer women were invited to the study in 1992-93 because of changes in the assembly of the research group, but as the participation rates were relatively high even in these examination years, the samples were included to analyses to provide analysis of risk factor levels in between regular time intervals. Some of the 38-year-old women were re-examined later as 50-year-olds and there were some individuals who were included in two cohorts but in that case, they were representing cross-sectionally different age groups.

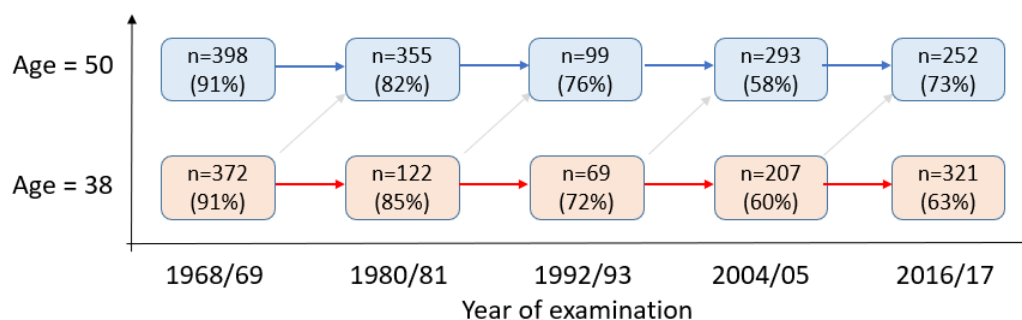


Figure 1. Numbers of 38- and 50-year-old participants (n) and participation rates (%) in Prospective Population Study of Women in Gothenburg in the five different cohort-years. Participation rates were relatively high, 58-91% over the entire study period.

Sampling methods and study design

The samples were obtained from the Revenue Office Register of Gothenburg and the selection method was based on dates of birth. All women in ages 38- and 50 years, living in Gothenburg and born on certain selected dates, were invited to a free health examination. As

the study collected even follow-up data, those who had earlier participated as 38-year-olds were invited to the follow-up examinations as 50-year-olds, but even new individuals were recruited continuously to both of these age groups as all women who fulfilled the criteria of age, the residence in Gothenburg and were born in the selected dates were invited, including the women who had moved to Gothenburg between examination years. Even women who had previously participated as 38-year-olds but moved from Gothenburg were invited to the examination at the age of 50. Difficulties in speaking or understanding Swedish language was the only exclusion criteria.

The study protocols were similar and comparable for all examinations between 1968 and 2017. Data from socio-economic status (SES), smoking habits, alcohol consumption, leisure-time physical activity (LTPA), diabetes and hypertension were collected by questionnaires. Weight, height, waist- and hip circumferences (WC, HC), and systolic- and diastolic blood pressures (SBP, DBP) were recorded at physical examination. Blood samples were drawn from the antecubital vein in fasting state. All data was entered into a database soon after the examinations and the individuals were coded with ID-numbers to anonymise participants. The study design and selection procedures of PSWG from 1968-69 to 2016-17 have been described more detailed previously.(25-27)

Assessment of cardiovascular risk factors

Anthropometric measurements: Height was recorded to the nearest 0.5 cm without shoes and body weight was measured with light indoor clothing recording to the nearest 0,1kg. BMI was calculated by using the height and weight measurements ($BMI = \text{weight (kg)} / (\text{height (m)})^2$). WC was measured in cm at the level of the umbilicus and HC was measured around the

widest part of buttocks, both with accuracy of 1 cm. Waist-hip ratio was calculated by using the waist- and hip circumferences ($WHR = WC/HC$).

Blood pressure: Systolic and diastolic blood pressures were measured by using a mercury manometer in seated position after 5min resting with the accuracy of 2mmHg. All individuals, including those with hypertension diagnosis or antihypertensive medication, were included as the elevated blood pressure values themselves present a cardiovascular risk rather than the hypertension diagnosis. Hypertension diagnosis and medication were based on Physician diagnoses (yes/no).

Blood samples: Total serum cholesterol, serum triglycerides and blood or plasma glucose were analysed according to standard methods of the laboratory of the Sahlgrenska University Hospital, Gothenburg.(28) Total s-cholesterol and s-triglycerides were given in mmol/L with accuracy of 0.1 and 0.01 mmol/L, respectively. HDL was measured for the first time in 1992-93 and the same analyse method was used even in the two following examinations 2004-05 and 2016-17, in unit “mmol/L” with accuracy of 0.1 mmol/L. LDL was calculated for 1992-93, 2004-05 and 2016-17 by using Friedewald’s equation “ $LDL = s\text{-cholesterol} - HDL - (0.45 * s\text{-triglycerides})$ ”, when s-triglycerides < 4.5, with all units in mmol/L. Glucose was measured in blood (b-glucose) in 1968-1993 and in plasma (p-glucose) in 2004-2017. B-glucose was converted to p-glucose by using the equation “ $p\text{-glucose (mmol/L)} = 1.11 * b\text{-glucose (mmol/l)}$ ” to establish a new, comparable variable “p-glucose” over the entire study period. This equation is valid when hematocrit and water concentrations are normal, which however could not be checked, and thus there is a risk for failure when comparing converted and original values of p-glucose. (29) Non-fasting individuals were excluded from glucose

analysis as clinically applicated reference intervals are defined for fasting values. Diabetes diagnosis and medication were based on Physician diagnoses (yes/no).

Smoking and usage of other tobacco products: The women were asked if they were currently smoking and how many cigarettes per day, quitted smoking and how many years ago or whether they had never smoked. The responses were categorised to 0-4 scale: 0=never smoker, 1=former smoker but not during the last 15 years, 2= former smoker but not during the last year, 3=quitted smoking during the last year and 4=current smoker, smoking at least one cigarette per day. Cigarette smoking was further dichotomised to two categories, “current smokers”, including category 4 and “never or former smokers”, including categories 0, 1, 2 and 3. Current usage of snus was asked at first time in 1992-93 by yes/no question forming the categories of “current usage of snus” (those responding “yes”) and “former or never using snus” (those responding “no”). Total usage of all tobacco products included cigarettes, cigars, pipe, snus, cigarette-cigarillos and e-cigarettes (e-cigarettes only from 2016-17), and those who responded “yes” to question of current use in at least one of these tobacco products were categorized into “current usage”, otherwise “never or former usage”.

Alcohol consumption: The women were asked, how often they were drinking beer, wine and spirits, respectively, whether they had never drunken alcohol, and whether they had quitted alcohol drinking and how long time ago in that case. The answers were classified into a 0-6 scale (0=never, 1=earlier, but not during the last 10 years, 2= earlier but not last year, 3=in a monthly basis, 4=weekly, 5=several times per week, 6=daily). The three types of alcohol beverage were merged into one to describe total alcohol consumption. “Abstainers” was defined as those who responded 0 or 1 or 2, but not 3 or higher to all of beer, wine and spirits

and “Drinking several times per week” category included those who answered 5 or 6 to at least one question regarding use of beer, wine or spirits consumption.

Leisure time physical activity: Validated “Saltin–Grimby Physical Activity Level Scale” was used when asking the participants to estimate their physical activity on leisure time on a 1-4 scale (1=mostly inactive, reading, watching TV etc., 2=intermediate activity at least 4h/week, walking, cycling etc., 3=high regular activity, jogging, gardening, etc., 4=very high activity, doing competitive sports).(30) In the analysis, the women were categorized into three activity levels, “Inactive”=1, “Moderate activity”=2 and “Regular exercise” =3 or 4.

Socio-economic status (SES): the women reported both their own and their husband’s employment level and were categorized into three socio-economic index (SEI) groups, taking the highest level of employment of women and their husbands into consideration. The SEI groups were coded by SEI 1=large-scale employers and officials of high or intermediate rank (highest SES), SEI 2=small-scale employers and lower-rank officials (middle SES) and SEI 3=skilled and unskilled workers (lowest SES)). This categorization method has been used even previously.(25)

Statistical methods

Statistical analyses and graphical illustrations were performed by using SPSS version 27. Significance level was set to $\alpha=0.05$. There were some individuals who were included in two different cohorts, firstly as 38- and later as 50-year-olds, but correlations between measurements of the same women did not need to be taken into account, because the analyses were strictly age-stratified, i.e. a same individual was representing respective age-groups

cross-sectionally only once. Thus, the samples were considered as un-paired when calculating p-values for differences between examination years in respective age groups.

Quantitative variables, including blood pressure, anthropometric measurements and blood samples: Mean values and standard deviations (SD) were calculated in 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17, stratified by age at examination (38 or 50 years of age).

Secular trends were explored by using linear regression models for continuous variables as a linear function of year of examination. Results were given in terms of regression coefficients over the entire study period from 1968-69 to 2016-17 and between the two latest examinations 2004-05 and 2016-17, respectively. A regression coefficient gives the mean change of variable over time (in unit or % per year) when the change is assumed to be linear over time. As the samplings occurred only in some specified years instead of a continuous period, this model includes a risk for misinterpretation of trend linearity. In aim to minimise the risk for misinterpretation, the assumption of linearity of secular trends was examined with graphical illustrations of 95% confidence intervals of measured values in each cohort year in respective age groups, presented in chronological order in the same figure (error bar plot in SPSS), to see whether respective variables were continuously increasing or decreasing over the entire time periods. The assumptions of large enough sample size (>50 individuals) and normal distribution of residuals were checked by descriptive tables and histograms, before calculating regression coefficients. If the residuals were not approximately normally distributed, a natural logarithm (Ln) was calculated to test whether it gave a residual distribution closer to normal curve, as illustrated in Figure 2. Ln from original variable was used to calculate secular trends, now given by %/year if logarithmized values gave a residual distribution closer to normal curve. This was the case for weight, WC and s-triglycerides.

The secular trends were always firstly examined with error bar plot figure with 95% CIs based on year-specific mean values, to see whether a linear trend was plausible. Then, the linear regression model was applied to give an effect size for the linear trend and a p-value.

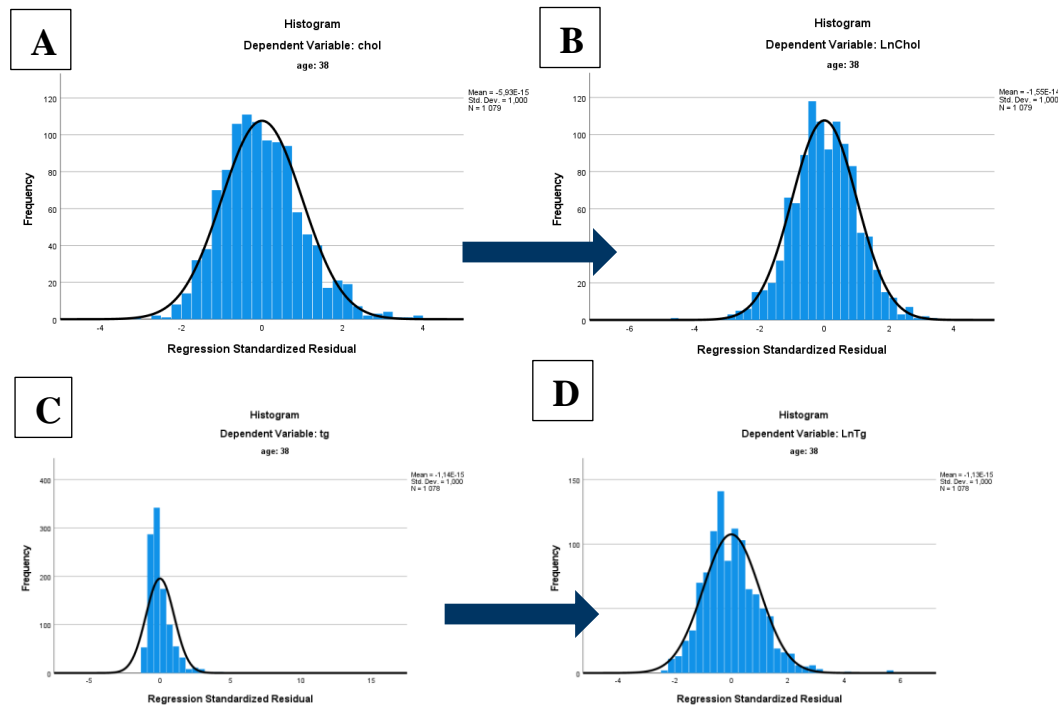


Figure 2: Example of histograms for checking the assumption of normal distribution of residuals in linear regression. A=original variable s-cholesterol, B=natural logarithm from s-cholesterol, C=original variable s-triglycerides and D=natural logarithm from s-triglycerides. For s-cholesterol, the original variable gave approximately normal distribution (A close to normal curve, B does not give better approximation), and therefore the original variable was used to calculate regr. coeff. for s-cholesterol. For s-triglycerides in contrast, the natural logarithm gave a distribution closer to normal curve (D better than C) and thus the logarithm of s-triglycerides was used instead of the original variable to get better model fit.

Categorical variables: Cross-tabulations were performed for categorical variables, including hypertension and diabetes diagnoses, smoking and tobacco usage, alcohol consumption and leisure time physical activity, to describe frequencies (%) of 38- and 50-year-old women in each predefined variable category cross-sectionally in 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17. The logistic regression model was used to calculate regression coefficients for

dichotomised variables in order to describe the mean change over time given by odds ratio/year. (odds ratio=OR=(odds for belonging to an outcome variable category)/(odds for not belonging to the outcome)), This model assumes the change in log-odds to be linear over a continuous period of time but as the samplings occurred only in some specified years instead of a continuous period, this model includes a risk for misinterpretation of trend linearity. In aim to minimise the risk for misinterpretation, linearity of secular trends was controlled with graphical illustrations of sector diagrams in each cohort year in respective age groups, presented in chronological order in a same figure, to see whether respective variables were continuously increasing or decreasing over the entire time periods. Secular trends were interpreted by checking both graphical illustration and p-values.

Adjustment for SES: Possible socio-economic inequalities (gradients) were checked cross-sectionally in 2004-05 and 2016-17 by comparing mean values of quantitative variables and OR of categorical variables between the highest SEI (SEI 1, reference category) and the two lower groups (SEI 2 and SEI 3). The most interesting trends between the two latest examinations in 2004-05 and 2016-17 were stratified by SES by calculating regression coefficients for each SEI group separately and analysing trends in SES sub-groups in the same way as was done for the entire samples of 38- and 50-year-olds.

Ethics

All subjects who participated in PSWG between 1968-2017 gave informed consent in accordance with the provisions of the Helsinki Declaration. Ethical approval was obtained from The Ethics Committee of University of Gothenburg for each examination cycle since 1980 (the latest

ethical approval 2016-17: 258-16 T853-16). Personal information was anonymized by number codes when entered into the database so that no individual person could be identified from the dataset.

Results

Anthropometric measurements and blood pressure

Table 1. shows mean values of anthropometric measurements and blood pressure, and frequencies of antihypertensive medication in 38- and 50-year-old women in the five different cohort years. Secular trends are described by regression coefficients (change/year) between 1968-2017 and between 2004-2017, respectively. Linearity of trends over time are graphically illustrated in Figure 3. Differences in mean values and trends between socio-economic index (SEI) groups between 2004-05 and 2016-17 are described in Table 5.

Body weight and height increased significantly in both 38- and 50-years-olds from 1968 to 2017 (weight 0.2 and 0.1%/year, and height 0.06 and 0.08 cm/year, respectively) but BMI increased significantly for only 38-year-olds (0.1%/year) during the same period. However, the increasing trends in weight, height, and BMI levelled off when comparing only the two most recent measurements 2004-05 and 2016-17.

Waist circumference (WC), hip circumference (HC) and waist-hip ratio (WHR) increased significantly from 1968 to 2017 in both age groups (WC 0.3 and 0.2%/year, HC 0.05 and 0.05cm/year, WHR 0.002 and 0.001/year). These increasing trends remained significant even between 2004-2017 with exception of WHR in 50-year-olds (WC 0.4 and 0.2%/year, HC 0.2 and 0.3cm/year and WHR 0.001/year, only in 38-year-olds). When analysing the three SEI

classes separately between 2004-05 and 2016-17, the increasing trends in WC remained significant only in the two highest SEI groups in 38-year-olds (0.5 and 0.4%/year in SEI 1 and SEI 2, respectively) but not in the lowest group or in any of SEI groups in 50-year-olds. In 38-year-olds, the two lowest SEI groups had significantly higher WC cross-sectionally in 2004-05 (4.1 and 6.1% higher means in SEI 2 and SEI 3, respectively, compared to the highest SEI), but there were no significant differences between different SEI groups in 2016-17. In 50-year-olds, the lowest SEI was associated with higher WC cross-sectionally in both 2004-05 and 2016-17 (7.1 and 8.9% higher means compared the highest SEI). As well, the increase of HC between 2004-17 was significant only in the two highest SEI groups in both ages (SEI 1: 0.25 and 0.28cm higher/year; SEI 2: 0.29 and 0.32cm higher/year in 38- and 50-year-olds, respectively), but not in the lowest SEI groups. In 38-year-olds, there were no differences in means of HC between different SEI groups cross-sectionally in 2004-05 or 2016-17 but in 50-year-olds, the lowest SEI group had significantly higher HC in both 2004-05 and 2016-17 (3.7 and 4.9cm) compared to the highest SEI group. Correspondingly, the increase in WHR remained significant between 2004-17 only in the highest SEI group in 38-year-olds (0.002/year) but not in any other groups or in older women. Lower SEI was associated with higher WHR cross-sectionally in 2004-05 in both age groups (SEI 2 and SEI 3 in 38-year-olds by 0.02 and 0.02/year, respectively and SEI 3 in 50-year-olds by 0.03/year), but in 2016-17, only in 50-year-olds (SEI 3 by 0.04/year), compared to the highest SEI.

Systolic and diastolic blood pressure decreased significantly in both age groups from 1968 to 2017 (-0.3 and -0.2mmHg/year) but these decreasing trends did not remain between the two most recent examinations 2004-05 and 2016-17 in exception of systolic blood pressure for 50-year-olds which decreased by 0.4mmHg/year. Only few individuals were using

antihypertensive medication during the entire study period (1-2% of 38-year-olds and 3-9% of 50-year-olds) and there were no significant changes in usage of antihypertensive medication over time.

Table 1. Means, standard deviations (SD) and regression coefficients for anthropometric measurements and blood pressure, and frequencies (%) of individuals using antihypertensive medication in 38- and 50-year-old cohorts in the 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17 examinations.

	Age (years)	<u>1968-69</u>		<u>1980-81</u>		<u>1992-93</u>		<u>2004-05</u>		<u>2016-17</u>		Regr. Coeff. (unit or % /year) 1968-2017	Regr. Coeff. (unit or % /year) 2004-2017
		n	mean(SD)	n	mean(SD)	n	mean(SD)	n	mean(SD)	n	mean(SD)		
<u>Weight(kg)</u>	38	372	63.4(11.2)	122	63.3(12.0)	69	64.8(10.2)	202	67.0(13.1)	320	68.2(13.6)	0.2%***	0.1%
	50	398	66.2(11.1)	355	66.3(11.6)	99	69.6(12.4)	292	68.7(12.1)	250	70.6(13.1)	0.1%***	0.2%
<u>Height(cm)</u>	38	372	165(6)	121	166(6)	69	166(6)	206	167(7)	321	167(7)	0.06***	0.01
	50	398	163(6)	355	164(6)	99	167(6)	292	166(6)	251	167(6)	0.08***	0.05
<u>BMI(kg/m²)</u>	38	372	23.4(3.8)	121	22.9(4.2)	69	23.6(3.3)	202	23.9(4.3)	320	24.3(4.6)	0.1%**	0.1%
	50	398	24.8(3.8)	355	24.7(4.0)	99	25.0(4.0)	292	24.8(4.3)	250	25.4(4.6)	0.0%	0.2%
<u>Waist(cm)</u>	38	372	71.6(8.2)	122	76.2(10.8)	68	76.5(9.2)	201	78.1(10.5)	321	81.9(11.1)	0.3%***	0.4%***
	50	397	74.8(8.7)	354	80.1(11.1)	98	80.2(12.3)	292	82.6(11.1)	251	84.8(11.6)	0.2%***	0.2%*
<u>Hip(cm)</u>	38	353	98.9(7.5)	121	96.6(8.9)	68	94.8(8.5)	201	98.7(8.5)	321	101.5(9.6)	0.05***	0.2**
	50	379	100.2(8.0)	355	99.2(8.4)	98	98.5(9.2)	292	99.9(8.5)	249	103.3(9.3)	0.05***	0.3***
<u>WHR</u>	38	353	0.73(0.05)	121	0.79(0.06)	68	0.81(0.05)	201	0.79(0.06)	321	0.81(0.06)	0.002***	0.001**
	50	378	0.75(0.05)	354	0.81(0.07)	98	0.81(0.07)	292	0.83(0.07)	249	0.82(0.07)	0.001***	0.0
<u>SBP (mmHg)</u>	38	372	123(15)	122	123(14)	69	118(14)	202	117(12)	320	116(12)	-0.2***	-0.1
	50	398	138(22)	354	135(21)	99	134(21)	291	128(17)	252	123(15)	-0.3***	-0.4**
<u>DBP (mmHg)</u>	38	372	81 (9.2)	122	83(9)	65	74(10)	190	74(9)	320	75(9)	-0.1***	0.1
	50	398	88(11)	354	87(10)	96	82(11)	271	79(9)	252	78(9)	-0.2***	-0.03
<u>Hypertension medication</u>		n	%	n	%	n	%	n	%	n	%	OR/year 1968-2017	OR/year 2004-2017
	38	372	1	122	1	69	1	207	2	321	2	1.00	0.96
50	398	5	355	7	99	9	293	7	252	3	1.00	0.94	

n refers to number of individuals included to the analyses. ***=p <0.001, **=p <0.01 and *= p <0.05 (significance level p<0.05). OR = odds ratio (odds for individuals using medication/ odds for individuals not using medication).

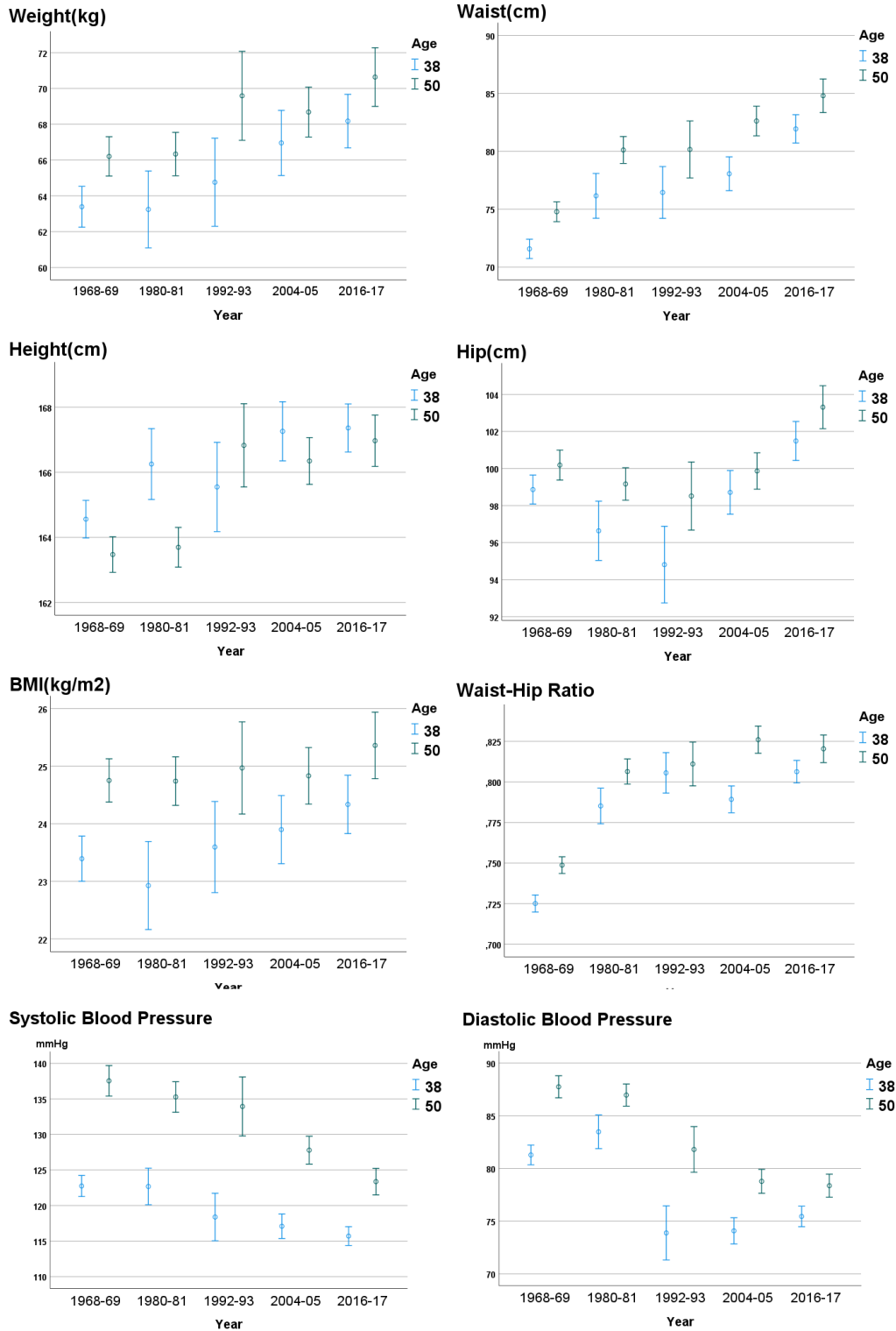


Figure 3. Mean values (95% CI) of weight, height, BMI, waist, hip, WHR, SBP and DBP versus year of examination in 38- and 50-year-old cohorts.

Blood lipids and plasma glucose

Mean values and regression coefficients (change/year) for blood lipids and plasma glucose, and the frequencies of antidiabetic medication and self-reported diabetes are presented in Table 2. Trends in mean values over time are graphically illustrated in Figure 4. Socio-economic disparities in mean values and trends between three different socio-economic index (SEI) groups between 2004-05 and 2016-17 are shown in Table 5.

Total serum cholesterol decreased significantly both among 38- and 50-year-olds over the entire study period 1968-2017 (-0.03 and -0.04mmol/L/year) but increased again between the two most recent examinations 2004-17 in both age groups (0.03 and 0.01mmol/L/year). However, after stratification by SES, the increasing trends in mean values of total cholesterol between 2004-17 remained significant only in the two highest SEI groups among 38-year-olds (0.04 and 0.03mmol/L/year in SEI 1 and SEI 2, respectively) and in the middle SEI group among 50-year-olds (0.03mmol/L/year). There were no differences in mean values of total cholesterol between the three different SEI groups cross-sectionally in 2004-05 or 2016-17 in any of ages.

Serum triglycerides decreased overall from 1968 to 2017 in both age groups (-0.5 and -0.5%/year) but increased significantly by 0.8%/year in 38-year-olds between the latest examinations 2004-2017. The increasing trend among 38-year-olds from 2004 to 2017 remained significant only in the middle SEI group (1.1%/year) but not in the highest and lowest SEI groups, and there were no significant trends among 50-year-olds when analysing the three SEI groups separately. The lowest SEI was associated to higher s-triglycerides in 50-year-olds cross-sectionally in 2004-05 (22%/year) but not in 2016-17, whereas there were no

significant differences in mean values of triglycerides between different SEI groups in 38-year-olds in 2004-05 or 2016-17.

Table 2. Mean and standard deviations (SD) for blood samples and diabetes, and frequency (% of all) of individuals with diabetes medication and self-reported diabetes in 38- and 50-year-old cohorts in the 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17 examinations.

	Age (years)	<u>1968-69</u>		<u>1980-81</u>		<u>1992-93</u>		<u>2004-05</u>		<u>2016-17</u>		Regr. Coeff. (unit or % /year) 1968-2017	Regr. Coeff. (unit or % /year) 2004-2017
		n	mean(SD)	n	mean(SD)	n	mean(SD)	n	mean(SD)	n	mean(SD)		
<u>Cholesterol (mmol/L)</u>													
	38	371	6.3(0.9)	121	5.7(1.0)	67	5.0(1.0)	204	4.6(0.8)	316	5.0(0.9)	-0.03***	0.03***
	50	398	7.2(1.1)	348	6.5(1.1)	91	5.8(1.0)	290	5.3(1.0)	247	5.5(0.9)	-0.04***	0.01*
<u>Triglycerides (mmol/L)</u>													
	38	371	1.1(0.4)	121	1.0(0.8)	66	0.9(0.4)	204	0.8(0.5)	316	0.9(0.5)	-0.5%***	0.8%*
	50	398	1.3(0.6)	348	1.2(0.6)	91	1.2(0.6)	291	1.0(0.5)	245	1.0(0.6)	-0.5%***	-0.1%
<u>HDL (mmol/L)</u>													
	38	-	-	-	-	62	1.5(0.4)	204	1.7(0.4)	317	1.8(0.4)	0.01***	0.004
	50	-	-	-	-	86	1.6(0.5)	290	1.8(0.5)	247	2.0(0.5)	0.01***	0.01***
<u>LDL (mmol/L)</u>													
	38	-	-	-	-	61	3.0(0.9)	204	2.5(0.7)	314	2.8(0.8)	0.003	0.03***
	50	-	-	-	-	85	3.6(0.9)	289	3.1(0.9)	244	3.0(0.8)	-0.02***	-0.001
<u>P-glucose (mmol/L)</u>													
	38	371	4.5(0.8)	121	4.3(0.5)	61	4.9(2.0)	190	4.6(0.7)	309	5.3(0.5)	0.02***	0.06***
	50	397	4.7(1.0)	349	4.6(0.5)	86	4.8(1.0)	259	4.8(0.6)	235	5.4(0.8)	0.01***	0.05***
<u>Diabetes med.</u>													
		n	%	n	%	n	%	n	%	n	%	OR/year 1968-2017	OR/year 2004-2017
	38	372	0.3	122	0	69	3	207	1	321	0.3	1.00	0.91
	50	398	1	355	0.3	99	0	293	0.3	252	1	1.00	1.10
<u>Self-reported Diabetes</u>													
	38	372	0.3	122	0	69	3	207	1	321	0.3	1.00	0.91
	50	398	1	355	0.3	99	2	293	1	252	1	1.00	1.00

n=number of individuals included in the analyses. ***=p <0.001, **=p <0.01 and *= p <0.05. OR = odds ratio.

HDL increased from 1992-93 to 2016-17 in both 38- and 50-year-olds (0.01mmol/L/year in both ages) but between 2004-2017, the increasing trend remained only in 50-year-olds (0.01mmol/L/year). The increasing trend among 50-year-olds between 2004-2017 remained significant only in the two highest SEI groups (0.02 and 0.01mmol/L/year), but there were no

significant trends among 38-year-olds when the three SEI groups were analysed separately. The lowest SEI was associated to lower HDL (-0.2mmol/L) among 50-year-olds in 2004-05 but not in 2016-17, and there were no significant differences in mean values of HDL between different SEI groups in 38-year-olds in 2004-05 or 2016-17. HDL-cholesterol was the only risk factor analysed this study where older cohorts had better mean values than the younger cohorts (1.8 and 2.0 mmol/L in 2016-17).

LDL decreased from the first measurement in 1992-93 to the following examination in 2004-05 in both age groups (Figure 2) but increased significantly by 0.03mmol/L/year in 38-year-olds between the two latest measurements in 2004-17. When stratified by SES, the increasing trend in LDL among 38-year-olds between 2004-17 remained significant only in the two highest SEI groups (0.03mmol/L/year in both SEI 1 and SEI 2), but not in the lowest SEI group. In 50-year-olds, the decrease of LDL 1992-2004 levelled off between the two latest examinations but overall, LDL decreased significantly by 0.02mmol/L/year from 1992 to 2017. There were no significant differences in mean values of LDL between the three different SEI groups cross-sectionally in 2004-05 or 2016-17 in any of ages.

P-glucose increased significantly both between 1968-2017 and 2004-2017 in both age groups and the highest increase occurred between the two most recent measurements 2004-05 and 2016-17. (0.02 and 0.01mmol/L/year between 1968-2017, 0.06 and 0.05mmol/L/year between 2004-2017). The increasing trends in mean values of p-glucose from 2004 to 2017 remained significant in all SEI groups in both 38- and 50-year-olds when adjusted for SES. The lowest SEI was associated to higher p-glucose compared to the highest SEI in both age groups in 2016-17 (0.1 and 0.4mmol/L) and among 50-year-olds in 2004-05 (0.2mmol/L). The

frequency of women taking antidiabetic medication was low during the whole study period (0.3-3% of 38-year-olds and 0-1% of 50-year-olds) and there were no significant changes in usage of antidiabetic medication.

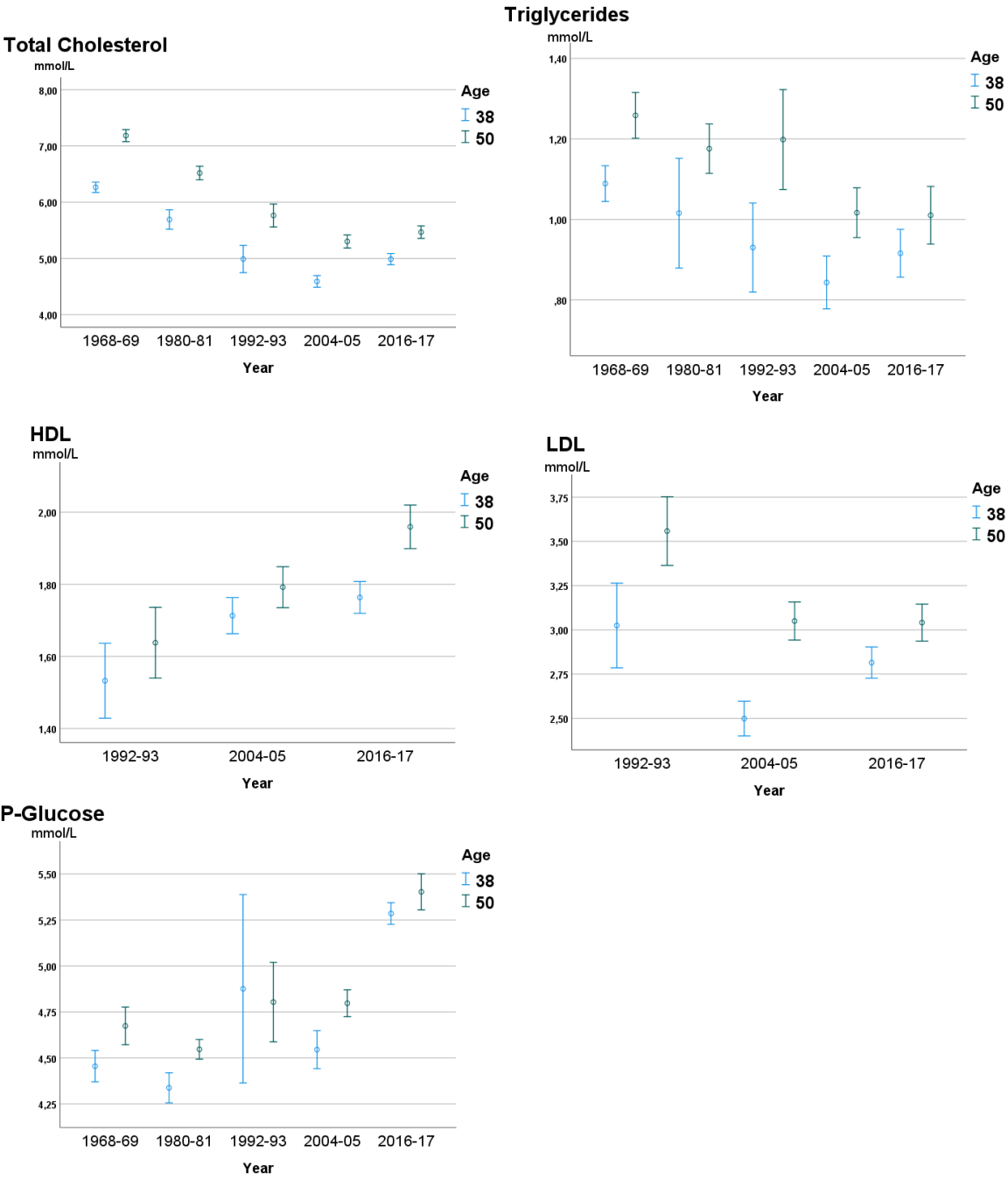


Figure 4. Mean values (95% CI) of total cholesterol, triglycerides, HDL, LDL and P-glucose in 38- and 50-year-old cohorts versus year of examination.

Behavioural risk factors

Tables 3 and 4 present the frequencies and trends in different tobacco and alcohol consumption categories, and leisure time physical activity categories, respectively. Figures 5, 6 and 7 illustrate proportions of women belonging to different categories of tobacco usage, alcohol consumption and leisure time physical activity, respectively. Table 6 describes socio-economic disparities in behavioural risk factors between three different socio-economic index (SEI) groups between 2004-05 and 2016-17.

Table 3. Frequencies of 38- and 50-year-old individuals in different smoking and alcohol consumption categories in the 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17 examinations.

	<u>1968-69</u>		<u>1980-81</u>		<u>1992-93</u>		<u>2004-05</u>		<u>2016-17</u>		<u>Regr.coeff.</u>	<u>Regr.coeff.</u>
	n	%	n	%	n	%	n	%	n	%	<u>OR/year</u>	<u>OR/year</u>
<u>Current cigarette smokers</u>												
38-year-olds	371	47	122	38	69	25	204	11	321	10	0.96***	0.99
50-year-olds	398	37	355	39	99	27	291	23	252	11	0.97***	0.93***
<u>Current users of snus</u>												
38-year-olds	-	-	-	-	68	4	200	8	320	10	1.03	1.00
50-year-olds	-	-	-	-	98	0	289	8	251	7	1.04	1.00
<u>Current users of any tobacco products</u>												
38-year-olds	372	47	122	38	69	30	204	18	321	21	0.97***	1.00
50-year-olds	398	37	355	39	99	30	291	28	252	16	0.98***	0.94**
<u>Alcohol abstainers</u>												
38-year-olds	372	21	122	13	69	10	203	8	321	18	1.00	1.10**
50-year-olds	397	26	355	20	99	6	289	8	250	12	0.97***	1.00
<u>Drinking alcohol several times per week</u>												
38-year-olds	371	29	122	24	69	12	202	16	320	12	0.98***	0.97
50-year-olds	396	29	355	15	99	33	285	27	250	22	1.00	0.98

n refers to number of individuals included to the analyses. “%” shows the frequency of given variable calculated out of n. ***=p <0.001, **=p <0.01 and *= p <0.05 (significance level p<0.05). OR = odds ratio.

Frequency of cigarette smokers decreased significantly from 1968 to 2017 in both 38- and 50-year-olds (OR 0.96 and 0.97/year) and the decreasing trend continued as significant in 50-year-olds even between 2004-17 (OR 0.93/year), but only in the middle SEI group (OR 0.90/year) after stratification by SES. The lowest SEI was associated with higher frequency of

cigarette smoking compared to the highest SEI in both age-groups cross-sectionally in 2016-17 (OR 10.03 and 4.56) as well as the two lowest SEI groups were among 50-year-olds, but not in 38-year-olds, in 2004-05 (OR 2.70 and 3.35).

Usage of snus from 1992 to 2017 seemed to increase in both 38- and 50-year-olds but there was no statistical significance for trends neither between 1992-2017 nor 2004-2017, and not either in any of SEI groups when they were analysed separately. Among 38-year-olds, the lowest SEI was significantly associated to higher frequency of snus usage compared to the highest SEI in 2004-05 (OR 5.17) but there were no significant differences between different socio-economic groups in 2016-17 among 38- or 50-year-olds or among 50-year-olds in 2004-05.

The frequency of current users of at least one of all tobacco products, including cigarettes, cigars, pipe, e-cigarettes or snus, decreased significantly in both 38- and 50-year-olds between 1968-2017 (OR 0.97 and 0.98/year), and the decreasing trend continued among 50-year-olds even between 2004-2017 (OR 0.94/year), but not in 38-year-olds. As for cigarette-smoking, the decreasing trend in overall usage of tobacco products among 50-year-olds from 2004 to 2017 remained significant only in the middle SEI group (OR 0.91) when adjusted for SES.

The frequency of alcohol abstainers decreased significantly overall from 1968 to 2017 in 50-year-olds (OR 0.97/year) but not in 38-year-olds whereas between the two latest examinations 2004-05 and 2016-17, the rate of non-drinkers increased in 38-year-olds (OR 1.10/year) but not in 50-year-olds. The trend of higher frequency of abstainers among 38-year-olds from 2004 to 2017 remained significant only in the lowest SEI group (OR 1.22/year) but not in the two highest groups after adjustment for SES. There were significantly higher frequencies of

abstainers in the lowest SEI group compared to the highest SEI among both ages cross-sectionally in 2016-17 (OR 6.24 and 10.83) as well as the two lowest SEI groups had in 2004-05 among 50-year-olds (OR 8.55 and 22.42), but not in 38-year-olds.

Over the entire study period 1968-2017, the proportion of women drinking alcohol several times per week decreased in 38-year-olds (OR 0.98/year) but not in 50-year-olds but there were no significant changes in high drinking between the two most recent examinations 2004-05 and 2016-17, even not when adjusted for the three different SEI groups. In 50-year-olds, significantly lower frequency of high alcohol consumption was observed among the lowest SEI group cross-sectionally both in 2004-05 and 2016-17 (OR 0.33 and 0.22), compared to the highest SEI group, but among 38-year-olds, there were no significant differences in frequencies of high drinking between the three SEI groups in the same years.

The frequency of inactivity on leisure time decreased both over the entire study period and between the two most recent examinations in both age groups and time periods. Also, the fraction of women with high activity level (regularly exercising) increased in both ages, both between 1968-2017 and between 2004-2017. After stratification by SES, the trend of less inactive women among 38- and 50-year-olds from 2004 to 2017 remained significant in all SEI groups among 38-year-olds but only in the highest SEI group among 50-year-olds. As well, the trends of higher frequencies of regularly exercising women among 38- and 50-year-olds from 2004 to 2017 remained significant only in the highest SEI group among 38-year-olds (OR 1.08/year) and in the two highest SEI groups among 50-year-olds (OR 1.07/year), but not in the lowest SEI groups. Among 38-year-olds, women with the lowest SEI were doing high regular exercise in significantly lower frequency (OR 0.44) compared to the highest SEI group cross-sectionally in 2016-17, but considering inactivity and high regular

exercising, there were no other significant differences between SEI groups in any of age groups in 2004-05 or 2016-17.

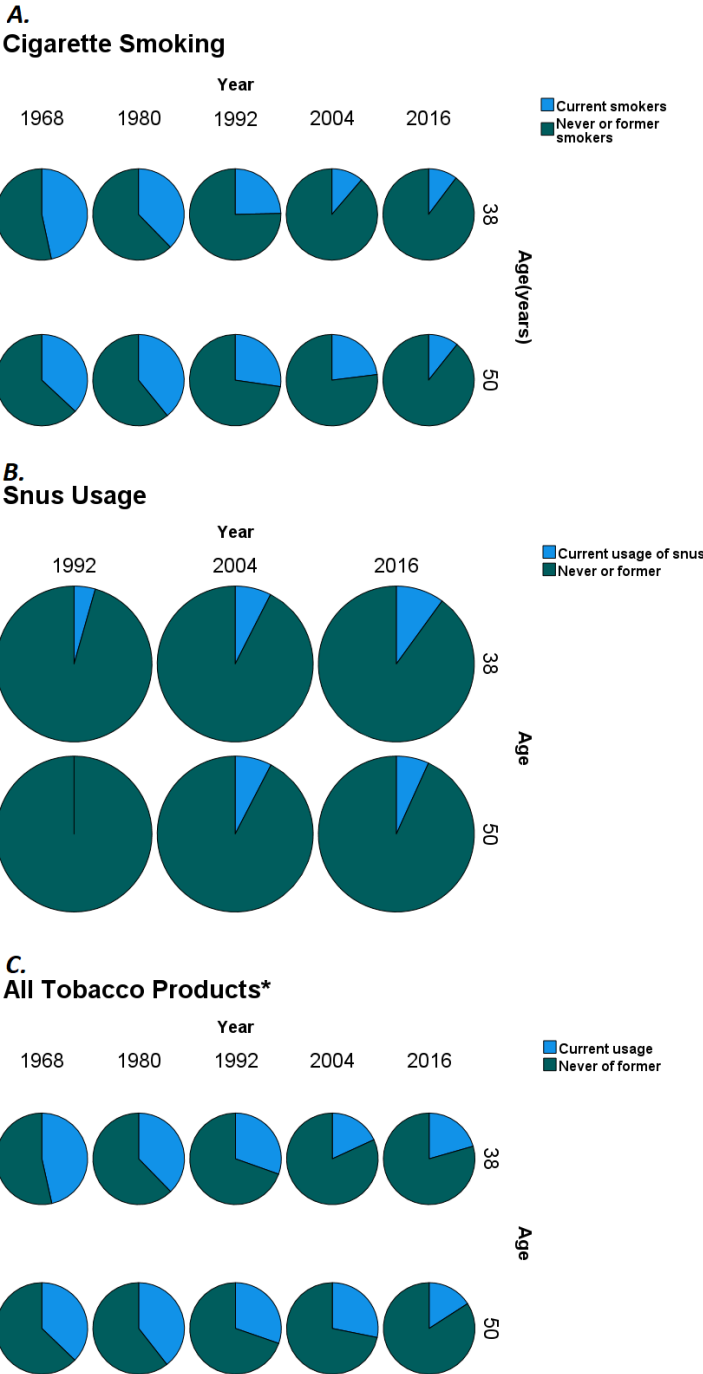
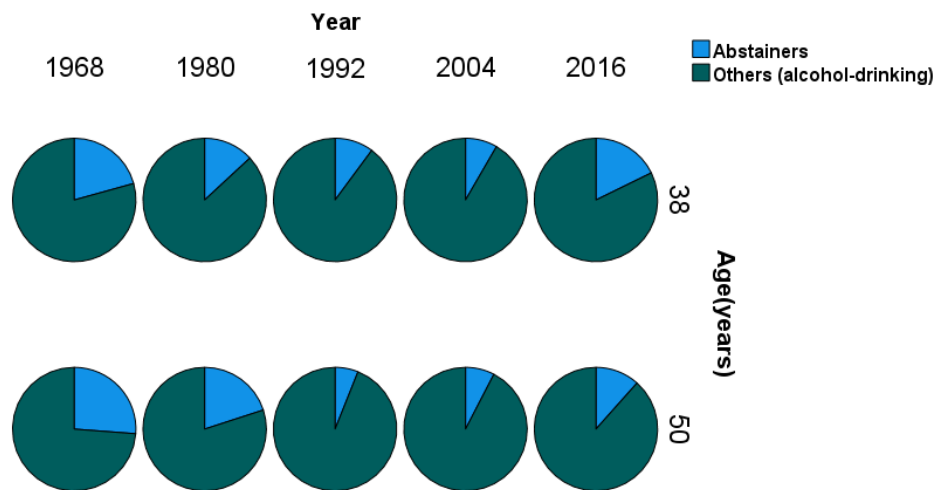


Figure 5. Proportions(%) of current usage of cigarettes (A), snus (B) and consumption of at least one of “all tobacco products”, including traditional inhaled tobacco products, snus and e-cigarettes (C) among 38- (upper rows) and 50-year-old (lower rows) women in 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17.

A. Alcohol Abstainers



B. High Alcohol Consumers

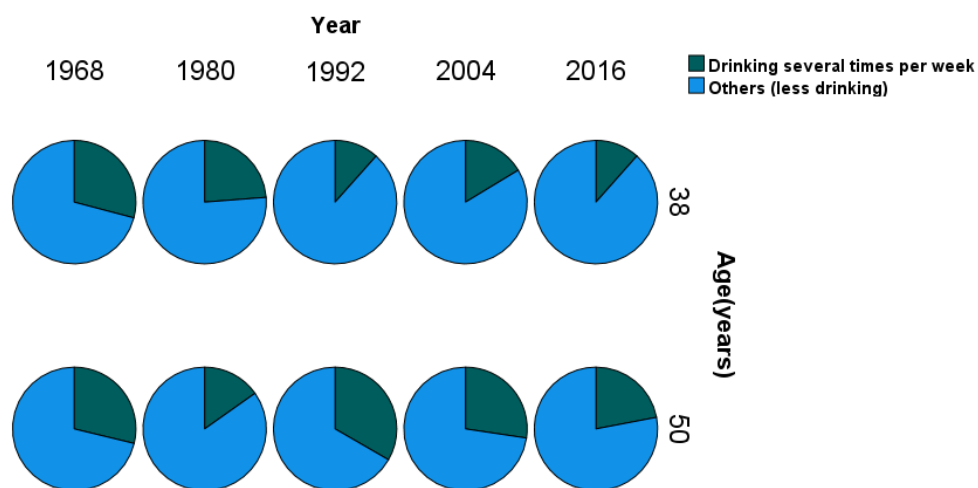


Figure 6. Proportions (%) of alcohol abstainers (A) and high alcohol consumers (B) among 38- (upper rows) and 50-year-old (lower rows) women in 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17.

Table 4. Number of women (n) within three leisure time physical activity categories, and frequencies (%) out of the whole cohort populations (N) in 38- and 50-year-old cohorts in the 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17 examinations.

	1968-69	1980-81	1992-93	2004-05	2016-17	Regr. Coeff. OR/year 1968-2017	Regr. Coeff. OR/year 2004-2017
<u>Leisure time physical activity</u>							
	n (%)	n (%)	n (%)	n (%)	n (%)		
<u>38-year-olds</u>							
Inactive	63(17)	42(34)	7(10)	46(23)	24(7)	0.99**	0.90***
Moderate physical activity	268(72)	51(42)	39(57)	74(36)	127(40)	0.97***	1.00
Regular exercise	41(11)	29(24)	23(33)	84(41)	169(53)	1.05***	1.04*
	N=372	N=122	N=69	N=204	N=320		
<u>50-year-olds</u>							
Inactive	71(18)	114(32)	21(21)	48(17)	25(10)	0.99***	0.95*
Moderate physical activity	266(67)	161(45)	51(52)	128(44)	80(32)	0.98***	0.96**
Regular exercise	60(15)	80(23)	27(27)	113(39)	146(58)	1.04***	1.10***
	N=397	N=355	N=99	N=289	N=251		

***=p <0.001, **=p <0.01 and *= p <0.05 (significance level p<0.05). OR = odds ratio.

Leisure Time Physical Activity

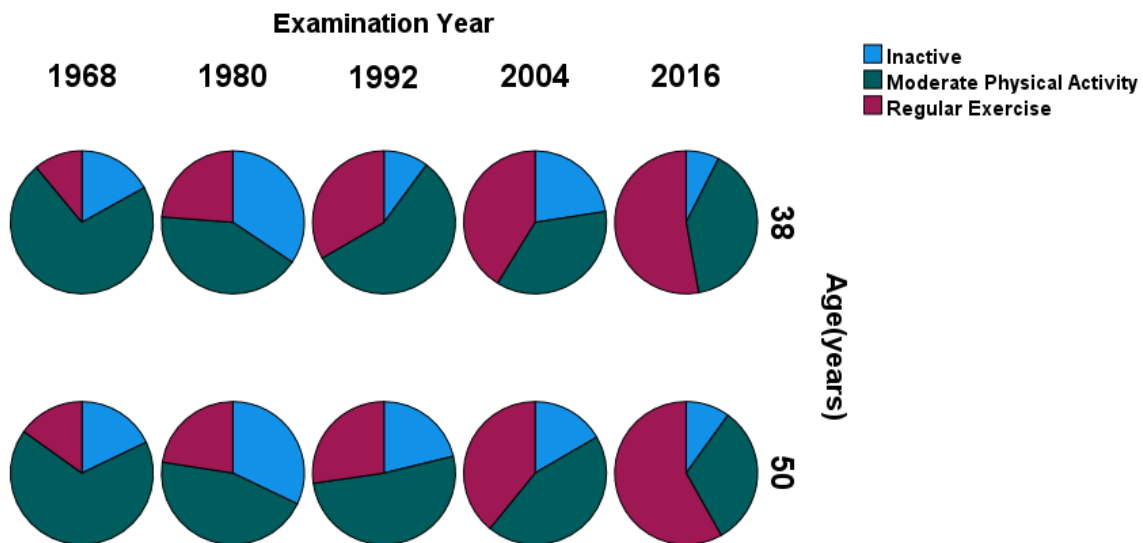


Figure 7. Proportions of 38- and 50-year-old women within the three leisure time physical activity categories in 1968-69, 1980-81, 1992-93, 2004-05 and 2016-17.

Table 5. part 1. (continues on the next page) The main findings in trends of quantitative outcome variables stratified by socio-economic status. Mean difference between SEI groups describe differences between the two lowest classes SEI 2 and SEI 3 compared to the highest group (SEI 1, Ref. = reference) cross-sectionally in 2004-05 and 2016-17, respectively. Regression Coefficients are calculated for each SEI group separately to describe significance for linear trends within respective socio-economic group.

Variable/Age	Mean difference between SEI groups in 2004-05 (unit or %, SEI 1=reference)	Mean difference between SEI groups in 2016-17 (unit or %, SEI 1=reference)	Trend linearity/ Regr. Coeff. 2004-17 (unit or %/ year)
<u>Waist(%)</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.5%***
SEI 2	4.1%*	2.7%	0.4%**
SEI 3	6.1%*	3.4%	0.3%
50-year-olds			
SEI 1	Ref.	Ref.	0.2%
SEI 2	0.5%	1.3%	0.3%
SEI 3	7.1%***	8.9%**	0.4%
<u>Hip(cm)</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.25*
SEI 2	1.8	2.3	0.29*
SEI 3	3.4	2.6	0.18
50-year-olds			
SEI 1	Ref.	Ref.	0.28**
SEI 2	0.6	1.1	0.32**
SEI 3	3.7**	4.9**	0.38
<u>WHR</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.002*
SEI 2	0.02*	0.01	0.001
SEI 3	0.02*	0.01	0.001
50-year-olds			
SEI 1	Ref.	Ref.	-0.001
SEI 2	-0.002	0.002	0.0
SEI 3	0.03*	0.04**	0.001
<u>Total cholesterol (mmol/L)</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.04***
SEI 2	0.1	0.01	0.03**
SEI 3	0.3	0.06	0.02
50-year-olds			
SEI 1	Ref.	Ref.	0.01
SEI 2	-0.03	0.1	0.03*
SEI 3	0.1	-0.09	-0.01
<u>Triglycerides (mmol/L)</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.6%
SEI 2	-0.4%	6%	1.1%*
SEI 3	12%	6%	0.0%
50-year-olds			
SEI 1	Ref.	Ref.	0.1%
SEI 2	3%	7%	0.4%
SEI 3	22%**	14%	-0.6%

Table 5. part 2

Variable/Age	Mean difference between SEI groups in 2004-05 (unit or %, SEI 1=reference)	Mean difference between SEI groups in 2016-17 (unit or %, SEI 1=reference)	Trend linearity/ Regr. Coeff. 2004-17 (unit or %/ year)
<u>HDL (mmol/L)</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.01
SEI 2	0.002	-0.1	0.001
SEI 3	-0.04	-0.1	0.01
50-year-olds			
SEI 1	Ref.	Ref.	0.02**
SEI 2	-0.04	-0.1	0.01*
SEI 3	-0.2 *	-0.1	0.02
<u>LDL (mmol/L)</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.03**
SEI 2	0.1	0.1	0.03**
SEI 3	0.2	0.1	0.02
50-year-olds			
SEI 1	Ref.	Ref.	-0.001
SEI 2	0.01 NS	0.1	0.01
SEI 3	0.2 NS	-0.1	-0.03
<u>P-glucose (mmol/L)</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.06***
SEI 2	0.2	0.2	0.06***
SEI 3	0.1	0.1*	0.06***
50-year-olds			
SEI 1	Ref.	Ref.	0.06***
SEI 2	0.1	-0.1	0.04***
SEI 3	0.2*	0.4*	0.07***

SEI=socio-economic index. SEI 1=large-scale employers and officials of high or intermediate rank, SEI 2=small-scale employers and lower-rank officials, SEI 3=skilled and unskilled workers. ***=p <0.001, **=p <0.01 and *= p <0.05 (significance level p<0.05).

Table 6. part 1. (continues on the next page). The main findings in trends of categorical outcome variables stratified by socio-economic status (SES). Differences between SEI groups are described by odds ratios (OR) of the two lowest classes (SEI 2 and SEI 3) compared to the highest group (SEI 1, Ref. = reference) cross-sectionally in 2004-05 and 2016-17, respectively. Regression coefficients given by OR/year between 2004-17 are calculated for each SEI group separately to describe significance for linear trends within respective SEI group.

Variable/Age	OR 2004-05 (Difference between SEI groups, SEI 1=reference)	OR 2016-17 (Difference between SEI groups, SEI 1=reference)	Regr. Coeff. (OR/year) 2004-17
<u>Cigarette smokers</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.91
SEI 2	0.83	2.20	0.99
SEI 3	1.38	10.03***	1.07
50-year-olds			
SEI 1	Ref.	Ref.	0.96
SEI 2	2.70**	1.28	0.90**
SEI 3	3.35**	4.56**	0.98
<u>Snus users</u>			
38-year-olds			
SEI 1	Ref.	Ref.	1.05
SEI 2	1.22	1.24	1.05
SEI 3	5.17*	2.27	0.98
50-year-olds			
SEI 1	Ref.	Ref.	1.02
SEI 2	1.14	0.54	0.96
SEI 3	1.82	1.37	1.00
<u>Users of any tobacco products</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.99
SEI 2	1.27	1.70	1.02
SEI 3	2.48	4.62***	1.95
50-year-olds			
SEI 1	Ref.	Ref.	0.97
SEI 2	1.98*	0.98	0.91**
SEI 3	2.72**	4.07**	1.00
<u>Abstainers</u>			
38-year-olds			
SEI 1	Ref.	Ref.	1.02
SEI 2	1.34	1.60	1.03
SEI 3	0.72	6.24***	1.22**
50-year-olds			
SEI 1	Ref.	Ref.	1.15
SEI 2	8.55*	1.95	1.02
SEI 3	22.42**	10.83***	1.09
<u>Drinking several times per week</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.97
SEI 2	0.57	0.66	0.98
SEI 3	0.60	0.56	0.96
50-year-olds			
SEI 1	Ref.	Ref.	0.96
SEI 2	0.66	0.89	0.99
SEI 3	0.33**	0.22*	0.93

Table 6. part 2.

Variable/Age	OR 2004-05 (Difference between SEI groups, SEI 1=reference)	OR 2016-17 (Difference between SEI groups, SEI 1=reference)	Regr. Coeff. (OR/year) 2004-17
<u>Inactive</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.88**
SEI 2	1.29	1.74	0.90**
SEI 3	2.29	2.16	0.88**
50-year-olds			
SEI 1	Ref.	Ref.	0.93*
SEI 2	0.93	1.43	0.96
SEI 3	1.17	2.75	1.00
<u>High regular exercise</u>			
38-year-olds			
SEI 1	Ref.	Ref.	1.08**
SEI 2	1.22	0.60	1.02
SEI 3	0.74	0.44*	1.03
50-year-olds			
SEI 1	Ref.	Ref.	1.07**
SEI 2	0.96	0.98	1.07**
SEI 3	0.75	0.76	1.07
<u>Snus users</u>			
38-year-olds			
SEI 1	Ref.	Ref.	1.05
SEI 2	1.22	1.24	1.05
SEI 3	5.17*	2.27	0.98
50-year-olds			
SEI 1	Ref.	Ref.	1.02
SEI 2	1.14	0.54	0.96
SEI 3	1.82	1.37	1.00
<u>Users of any tobacco products</u>			
38-year-olds			
SEI 1	Ref.	Ref.	0.99
SEI 2	1.27	1.70	1.02
SEI 3	2.48	4.62***	1.95
50-year-olds			
SEI 1	Ref.	Ref.	0.97
SEI 2	1.98*	0.98	0.91**
SEI 3	2.72**	4.07**	1.00
<u>Abstainers</u>			
38-year-olds			
SEI 1	Ref.	Ref.	1.02
SEI 2	1.34	1.60	1.03
SEI 3	0.72	6.24***	1.22**
50-year-olds			
SEI 1	Ref.	Ref.	1.15
SEI 2	8.55*	1.95	1.02
SEI 3	22.42**	10.83***	1.09

SEI=socio-economic index. SEI 1=large-scale employers and officials of high or intermediate rank, SEI 2=small-scale employers and lower-rank officials, SEI 3=skilled and unskilled workers. ***=p <0.001, **=p <0.01 and *= p <0.05 (significance level p<0.05).

Discussion

Discussion of the results

The main findings of this study are the remaining concern of overweight and rising plasma glucose levels, but on the other hand the more beneficial trends in increased leisure time physical activity. WC increased significantly in both age groups, both over the whole study period and between the two latest measurements, demonstrating a remaining concern of central adiposity. Previous studies from both Western Swedish Gothenburg and Northern Sweden have observed similar results with increasing overweight among middle-aged women during the past decades (31, 32), but the increasing obesity is well-recognized issue even world-wide, reaching today pandemic levels.(33) In our study, WC and WHR were higher in the lowest socio-economic groups cross-sectionally in 2004-05, but between the two latest examinations in 2004-05 and 2016-17, there was a significant increase in WC (and WHR in 38-year-olds) only in the highest socio-economic groups. Thus, the gap between different socio-economic groups levelled off and the concern of obesity seems to consider now equally all socio-economic groups. Unfortunately, the results of this study are mainly descriptive and further analysis about associations between obesity and other life-style related variables, such as diet, cultural norms and mental health, should be made to better address the possible explanations for still increasing adiposity.

Alongside with the increasing WC, the levels of p-glucose increased markedly overall and especially between the two most recent examinations in all socio-economic groups, giving a critical concern for increasing frequency of impaired glucose tolerance and diabetes. Ulmer et al observed similar results in a large Austrian population study where fasting glucose levels increased markedly from 1985 to 2005 in both genders and all ages, including in total 1

81 350 individuals in ages of 20 to 79 year.(34) However, the rising glucose levels are not only an issue of single countries as WHO's national health registers have shown increasing fasting glucose levels and diabetes prevalence in almost all European countries since 2000.(4)

Favourably, total cholesterol and s-triglycerides decreased significantly in both age groups between 1968 and 2017 but concerningly, total cholesterol increased in both age groups as well as LDL and triglycerides increased in 38-year-olds again between the two latest measurements 2004-05 and 2016-17. The trends in total cholesterol levels are consistent with observations from Swedish Västerbotten, where total cholesterol decreased among 30 to 60-year-old women from 1990 to 2007 but in reverse, increased again between 2008-2010.(35) In 38-year-olds, the latest harmful trends of increased LDL and triglycerides considered only the highest socio-economic groups, simultaneously with increasing WC and WHR, indicating for possible relation between increasing obesity and more unbeneficial blood lipid levels in the highest SEI groups. As the harmful changes in LDL and triglycerides occurred only between the latest measurements, it is important to continue monitoring them even in the future to be able to make more evident conclusions about the trend direction.

Fortunately, there was a more beneficial trend in 50-year-olds as HDL increased between the two most recent examinations, however only in the two highest socio-economic groups. This might be partly due to beneficial effect of increased regular exercise, which was observed in both age groups, both over the entire study period and between 2004-2017, but after stratification by SES, only in the highest SEI groups. Correspondently, in 50-year-olds, the frequency of total inactivity decreased, but only in the highest SEI group whereas in 38-year-olds, the same beneficial trend considered all the three socio-economic groups. Thus, the

improvements in physical activity considered mainly the highest socio-economic groups, demonstrating a socio-economic gradient. Waller et al studied socio-economic differences in physical activity among 38- and 50-year-old women in PSWG between 1980-2005 and found no differences between socio-economic groups concluding that all socio-economic groups had increased their physical activity equally with unchanged socio-economic gaps.(36) Therefore, our results are signalling from a new unwanted change against wider socio-economic gaps in improvements in physical activity.

Cigarette smoking continued to decrease in 50-year-olds between 2004-17 but only in the middle socio-economic group and the frequencies of cigarette smoking were still relatively high in 2016-17 (10% and 11%). Similar trends have been observed even in Northern Sweden as the prevalence of smoking among 25-64-year-old women decreased from 26% in 1986 to 12% in 2009.(37) European Cardiovascular statistics are also consistent with our results as smoking decreased considerable in Northern and Western Europe from 1993 to 2014.(4) As observed previously, low socio-economic status was associated with higher frequency of cigarette smoking in both age-groups even at the most recent examination 2016-17 and the socio-economic gradient in smoking habits seems to be a remaining issue. Usage of snus have been increasing since 1992-93, however with no statistical significance, but it might develop into a new harmful trend and is important to monitor in the future.

A trend of higher frequency of alcohol abstainers was observed among 38-year-olds between 2004-2017 but this beneficial trend considered only the lowest socio-economic group.

Concerningly, the rates in drinking several times per week did not change and remained still relatively high (12% in 38-year-olds and 22% in 50-year-olds). Bloomfield et al investigated

social inequalities in alcohol consumption in a large international study, including 15 countries, and reported similar results as lower education was associated to higher frequency of alcohol abstention in Sweden but interestingly, not in other Nordic countries whereas higher education was related to heavy drinking in Germany, The Netherlands, France, Switzerland, and Austria.(38) Thus, there seems to be a tendency of those with higher socio-economic status to drink more which is important to recognize, as higher alcohol consumption might be a consequence of the improvement of women's status and educational level which have occurred during the past decades.

Strengths and weaknesses

The strengths of PSWG and this study are a long study period with relatively high participation rate (58-91%) over the entire study period. Unfortunately, the participation rates were declining during the later years being a possible source of bias as study participants often tend to have healthier lifestyles than non-participants. However, the participation rates in the two latest examination cycles 2004-05 and 2016-17 were relatively close to each other (58-73 and 60-63% in 38- and 50-year-olds, respectively), providing comparable samples when examining the latest trends between 2004-17. On the other hand, declining participation rates might affect more the results in long-term trends over the entire study period, giving false healthier risk factor levels in the later years and stronger trend estimations than the real changes in the population have been.

The study protocols were kept similar over the whole period to ensure high comparability, but some variables were slightly changed over the years. For example, glucose was initially measured in blood until 1992-93 and later in plasma, and the conversion may not be

completely accurate in all cases. However, the most remarkable increase in glucose levels occurred between 2004-05 and 2016-17, when glucose values were measured in the same units, supporting a real increase rather than a misinterpretation due to lack of comparability.

Additionally, as the study was ongoing over five decades, there were several different physicians doing the examinations so that the examination may not have occurred in the same way every time. As well, there might have been differences in laboratory methods used in analysis of blood but unfortunately, that is difficult to estimate afterwards. The information collected via questionnaires is based on the answers of the participants and includes recall-bias which might be affected by different socio-cultural environments as the times were changing.

Overall, this study provides broad description of secular trends in 38- and 50-year-old women in Gothenburg between 1968-69 and 2016-17, including socio-economic differences.

However, the observed trends were not adjusted for other variables such as physical activity level, dietary factors or mental stress, and further analysis are needed to study the associations in the background of the observed trends.

Conclusions and implications

Waist circumferences and plasma glucose levels increased in 38- and 50-year-old women, giving a remaining concern of raised metabolic risk considering all socio-economic groups.

The women became more active on leisure time but unfortunately mainly in the highest socio-economic groups during the later years, leaving a demand in reaching higher activity level even among those with lower SES. Due to these results, it is important to target health care

actions and political decisions in aim to decrease overweight and metabolic risk factors as well as to promote physical activity in all socio-economic groups.

CVDs are still the main cause of death in Swedish women, causing both individual suffering and economical costs for society. As CVDs are highly preventable, in primary with healthy lifestyle and, in the case of hypertension and hyperlipidaemia, secondarily with medicines, knowledge about risk factor prevalence in population is important to be able to direct the political decisions and health care resources. This study describes prevalence and trends for several key risk factors but there is still a big question remaining about why the risk factors have changed over time and further association-analysis are needed to study relationships between different risk factors as well as environmental factors. Furthermore, it is important to continue documentation of secular trends of cardiovascular risk factors to follow directions of the trends with special interest against the most recent trends of increased cholesterol in all women as well as increased LDL and triglycerides in 38-year-olds, to see whether they will continue in a harmful direction. However, although this study did not find significant trends in certain risk factors, it is important to continue monitoring of all key risk factors to see whether the reached beneficial risk factor levels will remain even in the future.

Populärvetenskaplig sammanfattning

Fem decennier av riskfaktorer för hjärtkärlsjukdomar hos kvinnor i Göteborgs Kvinnoundersökning från 1968-69 till 2016-17

Hjärtkärlsjukdomar är fortfarande idag den vanligaste dödsorsaken hos kvinnor i Sverige. Den viktigaste orsaken till dessa sjukdomar är åderförkalkning, en inflammatorisk process där det onda LDL-kolesterolet samlas in i kärlväggen och orsakar en förträngning i blodkärl med efterföljande minskad cirkulation till de drabbade organen, i vanligaste fall till hjärta eller hjärna. Åderförkalkning bidrar även till ökad risk för blodproppsbildning, vilket kan leda till hjärtinfarkt om proppen fastnar i hjärtats kärl och till stroke detta sker i hjärnans kärl. Det finns flera välkända förebyggingsbara riskfaktorer som påskyndar åderförkalkning innefattande rökning, otillräcklig fysisk aktivitet, hög alkoholkonsumtion, ohälsosam kost, fetma, högt blodsocker och diabetes, högt blodtryck, höga kolesterolvärden samt låg socio-ekonomisk status.

Denna studie beskriver utveckling av de viktigaste riskfaktorerna bland 38- och 50-åriga kvinnor som deltog i Kvinnoundersökningen i Göteborg i åren 1968-69, 1980-81, 1992-93, 2004-05 och 2016-17. Totalt 2488 kvinnor deltog genom åren i frivillig hälsoundersökning med kroppsundersökning, blodprovstagning och intervjuer.

Över hela perioden 1968-2017, ökade midjemåttan och blodsockernivåerna både hos 38- och 50-åriga. Denna utveckling gällde alla socio-ekonomiska grupper och den ökande trenden fortsatte även mellan 2004-2017, talande för kvarstående bekymmer för övervikt och diabetes. Positivt var att blodtrycket och kolesterolnivåerna sjönk, rökning minskade och fysisk aktivitet ökade under samma period. Dock visade analyser av trender mellan 2004-2017 att ökad fysisk aktivitet gällde delvis inte de lägre socio-ekonomiska grupperna och att

kolesterolnivåerna ökade igen mellan de senaste mätningarna i båda åldrar. Enligt dessa resultat, borde sjukvården och politiska beslut riktas till att åtgärda ökande övervikt som är även nära relaterat till höga blodsocker och kolesterolnivåer. Eftersom hjärtkärlsjukdomar innebär ett stort lidande till individer och efterföljande ekonomiska samhällskostnader, är det viktigt att fortsätta följa riskfaktorer i populationen för att kunna rikta förebyggande åtgärder och minska dödlighet i hjärtkärlsjukdomar i framtiden.

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