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Body weight at age 20 and in midlife is more important than weight gain for coronary atherosclerosis: Results from SCAPIS

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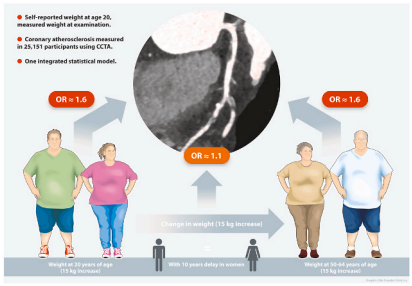
HIGHLIGHTS

- Weight at age 20 and in midlife is strongly related to coronary atherosclerosis.
- Weight gain from age 20 until midlife is modestly related to coronary atherosclerosis.
- There is no sex difference in the relation between weight and coronary atherosclerosis.
- Weight control programs in early adulthood may reduce cardiac disease later in life.

GRAPHICAL ABSTRACT



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ABSTRACT

Background and aims: Elevated body weight in adolescence is associated with early cardiovascular disease, but whether this association is traceable to weight in early adulthood, weight in midlife or to weight gain is not known. The aim of this study is to assess the risk of midlife coronary atherosclerosis being associated with body weight at age 20, body weight in midlife and body weight change.
Methods: We used data from 25,181 participants with no previous myocardial infarction or cardiac procedure in the Swedish CArdioPulmonary bioImage Study (SCAPIS, mean age 57 years, 51% women). Data on coronary atherosclerosis, self-reported body weight at age 20 and measured midlife weight were recorded together with potential confounders and mediators. Coronary atherosclerosis was assessed using coronary computed tomography angiography (CCTA) and expressed as segment involvement score (SIS).
Results: The probability of having coronary atherosclerosis was markedly higher with increasing weight at age 20 and with mid-life weight ($p < 0.001$ for both sexes). However, weight increase from age 20 until mid-life was only modestly associated with coronary atherosclerosis. The association between weight gain and coronary atherosclerosis was mainly seen in men. However, no significant sex difference could be detected when adjusting for the 10-year delay in disease development in women.
Conclusions: Similar in men and women, weight at age 20 and weight in midlife are strongly related to coronary atherosclerosis while weight increase from age 20 until midlife is only modestly related to coronary atherosclerosis.

1. Introduction

Obesity is a well-known risk factor for future coronary heart disease (CHD), although its power as a risk factor declines with age [1]. In most epidemiological studies, body weight or body mass index (BMI) is measured in adulthood, usually in midlife and shows a robust association with incident CHD [2].

Studies on weight in early adulthood (in this context defined as 17–25 years of age) typically show an increased risk of subsequent CHD associated with increased weight in most [3–9], but not all studies [10]. This is true whether body weight has been directly measured [3,5,9,11] or retrospectively self-reported [4,6–8]. Whether this is due to further weight gain during the life course, or to an effect of high early body weight, or a combination of both, is not well studied. The average weight gain from early adulthood to midlife is usually in the 10–15 kg range [10,12,13], and a recent metanalysis shows that even a very moderate weight gain of around 5 kg is associated with an 18% increase in risk of CHD [14].

The importance of weight change from early adulthood on subclinical markers of atherosclerosis has been addressed in only a few studies. Using carotid artery intima-media thickness (IMT), Stevens [13] showed that both BMI in early adulthood and weight gain until midlife related to midlife IMT in the ARIC study [13]. In the CARDIA study, Lee [15] corroborated the positive association between weight in early adulthood, further weight changes and adult IMT. However, using coronary artery calcification score (CACS) as a marker of subclinical coronary atherosclerosis, surprisingly, weight gain from early adulthood to midlife was associated with lower risk of CACS [15].

The aim of the current study was to assess whether the risk of midlife coronary atherosclerosis (50–64 years of age) is associated with self-reported weight at age 20, weight in midlife and weight gain between the two measurements. We used data on coronary atherosclerosis measured using coronary computer tomography angiography (CCTA) in subjects enrolled in the Swedish CArdioPulmonary bioImage Study (SCAPIS) [16,17].

2. Materials and methods

2.1. Study cohort

The Swedish CArdioPulmonary bioImage Study (SCAPIS) is a collaborative project involving six Swedish universities with a study population of 30,154 individuals aged 50–64 years aiming to update current knowledge about risk factors for cardiovascular diseases, with emphasis on the added value of imaging in risk prediction. Participants were randomly selected from the inhabitants of the Swedish cities of Malmö, Gothenburg, Stockholm, Uppsala, Umeå and Linköping and invited to a comprehensive examination as previously described [16]. The study was approved as a multi-center study by the regional ethical review board in Umeå (2010-228-31 M). The participants gave their written informed consent and all procedures adhered to the Declaration of Helsinki.

Exclusion criteria followed those described in our previous publication [17]. In brief, individuals were excluded from the present analyses if they did not undergo cardiac computed tomography (CT) or CCTA respectively or if there was major technical failure in reading CT or

CCTA. Individuals were also excluded if they had previously had a myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. There were several reasons for excluding individuals with previous CHD; i/ the focus of the current paper is preclinical coronary atherosclerosis; ii/ interventions due to prevalent CHD makes a standardized reading of cardiac CT and CCTA more difficult and iii/ prevalent CHD introduces treatment that may affect our associations.

2.2. Study procedure

Study procedures have been described in detail previously [16], briefly, information on self-reported weight at age 20 was collected from a questionnaire, as well as information on smoking habits, alcohol intake (AUDIT), educational level and treatment of hypertension, hyperlipidemia and diabetes. Midlife body weight at the physical examination in SCAPIS was measured on a balance scale with subjects dressed in light indoor clothing without shoes. Body height was measured to the nearest centimetre. Information on physical activity was retrieved from accelerometers using data on % of awake time spent in moderate or vigorous activity.

Systolic and diastolic blood pressures were measured in supine position twice in each arm with an automatic device (Omron M10-IT. Omron Health care Co. Kyoto. Japan) using the mean of systolic and diastolic blood pressure from the arm with the higher mean systolic blood pressure.

A venous blood sample was collected from participants after overnight fasting and used for immediate analysis of total cholesterol, LDL-C (low density lipoprotein cholesterol, calculated using the Friedwalds formula), HDL-C (high density lipoprotein cholesterol) and triglycerides and plasma glucose.

2.3. Imaging and image analyses

2.3.1. CT and CCTA

Cardiac imaging in SCAPIS has been described in detail previously [16]. Briefly, CT was performed using a dedicated dual-source CT scanner equipped with a Stellar Detector (Somatom Definition Flash, Siemens Medical Solution, Forchheim, Germany). Images for analyses of coronary artery calcifications (CAC), were obtained using electrocardiogram-gated non-contrast CT imaging at 120 kV. In preparation for CCTA imaging, renal function was assessed, potential contraindications identified, and a β-blocker (metoprolol) and sublingual glyceryl nitrate were given. The contrast medium iohexol (GE Healthcare, 350 mg I/mL) was administered at a dose of 325 mg I/kg body weight. CCTA was performed at 100 or 120 kV using five different protocols depending on heart rate, heart rate variability, presence of calcifications, and body weight.

All 18 coronary artery segments were visually examined for the presence of plaques as previously described [17]. Per-segment status of the coronary vessel was defined as: no atherosclerosis; 1–49% stenosis; ≥50% (i.e. significant) stenosis. Luminal obstruction was defined by visually estimating diameter stenosis (using the average of the longest and shortest diameter at the site of stenosis). Individuals were classified based on the highest degree of stenosis present in the coronary artery circulation.

For analyses of CCTA data, individuals were excluded if they did not undergo CCTA or if there was a technical failure in reading any of the four proximal segments (proximal right coronary, left main, proximal left anterior descending, and proximal circumflex artery) on the CCTA images. For analyses of CACS, individuals were excluded if they did not undergo non-contrast CT examination or if there was a technical failure in reading CT. Individuals were excluded from all analyses if they previously had had a myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting recorded as previously described [17].

For the main analyses, total coronary atherosclerotic burden was calculated using the segment involvement score [18,19] (SIS), a measure of the total number of coronary segments with atherosclerosis irrespective of degree of stenosis. For secondary analyses, we also calculated a modified version of the Duke prognostic coronary artery disease (CAD) score in which both extent and severity of atherosclerosis is weighed on a 7-grade scale (see Supplemental Material and [19]). For further secondary analyses, using the non-contrast enhanced CT images, the calcium content in each coronary artery was measured and summed to produce a total Agatston coronary artery calcification score (CACS) according to international standards [20]. Analyses were done using the raw outcome variables, but the results are presented in figures as the conditional probability of exceeding the following cut-off's that have been frequently used: SIS >0 and ≥ 4, Duke score >0 and ≥ 2 and CACS >0 and ≥ 100 [18,19,21,22].

2.3.2. Statistics and data analyses

SIS, Duke score and CACS all had distributions in which almost half the population has zero and then values are skewed to the right (Supplement Figs. S2–S4). In order to treat SIS as a continuous variable, we used a cumulative probability model (CPM) with a logit link function, described in detail in Ref. [23]. The CPM estimates the conditional cumulative distribution function as opposed to the conditional mean value in a linear model or conditional quantiles in quantile regression. This enables efficient mean, and quantile estimates while also allowing the exceedance probabilities for arbitrary values of the outcome to be estimated from a single model. Model fit was visually examined by a quantile-quantile plot of the probability-scale residuals [24] from the CPM which should follow a uniform distribution.

The proposed relationships between body weight at different ages and mid-life SIS are outlined in the directed acyclic graph (DAG) in online supplement (Fig. S1). The model created (Model 1) included weight at age 20 and weight at the examination as well as sex interactions to obtain sex-specific estimates. Adjustments were also made for site, age, height, LDL cholesterol, current smoking (Yes, No), frequency of alcohol intake estimated using AUDIT, attained education level (Did not finish elementary school, Elementary school, High school, University degree) and physical activity measures (time spent sedentary and time spent in moderate or vigorous activity). The analyses were based on imputed data (see below) but complete case analyses were also performed (Model 2). In a third model (Model 3), additional adjustments were made for potential mediators; systolic blood pressure, type 2 diabetes, treatment for hyperlipidemia and hypertension. As previously described [25], interaction between self-reported weight at 20 years and measured weight at the examination was tested once the additive model was built. Each continuous variable was modelled using restricted cubic splines with three interior knots. The associations are presented as odds ratios (OR) with an OR >1 indicating a higher probability of having higher SIS values. The OR for higher SIS was calculated for a weight increase of 15 kg, which was the approximate mean weight gain in both sexes from age 20 until examination. The associations were visualized by graphing the adjusted probability of having higher SIS evaluated at three starting weights at age 20, roughly corresponding to the sex-specific 10th, 50th and 90th percentiles of the distribution of weight at age 20. The associations were also visualized as the bivariate distributions of weight at age 20 and weight at mid-life examination and probability of having SIS above two different thresholds (SIS ≥0 and SIS ≥4) per sex. Weight gain was not included as a separate variable in the model, however, its association with SIS was evaluated by contrasting the estimated log odds for different combinations of weight at age 20 and weight at examination at a fixed weight gain of 15 kg.

Demographic and clinical characteristics of the main study population are presented without imputations. The pattern of missing predictor values was assessed using hierarchical cluster analysis with the pairwise proportion of observations being missing simultaneously among all pairs of variables. Participants were given the option of not responding to

Table 1
Basic characteristics of the SCAPIS participants without established CHD who underwent successful CCTA.

	Overall	Female	Male
n (%)	25,181	12,738	12,443
Age at examination (years)	57.3 (53.6, 61.1)	57.3 (53.6, 61.1)	57.3 (53.5, 61.1)
Weight at age 20[a] (kg)	65.0 (56.0, 75.0)	57.0 (52.0, 63.0)	74,0 (68,0, 80,0)
Weight at examination[b] (kg)	79.0 (68.7, 89.5)	70.0 (63.0, 79.3)	86.4 (79.0, 95.5)
Weight increase, age20-examination (kg)	13.4 (7.0–22.1)	13.0 (6.8–21.8)	13.9 (7.4–22.9)
Height at examination (cm)	172 (165, 180)	166 (161, 170)	180 (175, 184)
BMI (kg/m^2)	26.2 (23.9, 29.1)	25.5 (23.0, 28.39)	26.8 (24.7, 29.4)
Waist (cm)	94 (85, 102)	88 (80, 96)	98 (92, 105)
Waist/Hip	0.92 (0.85, 0.98)	0.86 (0.81, 0.91)	0.97 (0.93, 1.00)
Smoking			
Current	3079 (12.6)	1584 (12.8)	1495 (12.5)
Former	8790 (36.1)	4794 (38.8)	3996 (33.3)
Never	12,500 (51,3)	5983 (48,4)	6517 (54,3)
Highest grade of education			
Did not finish elementary school	142 (0.6)	64 (0.5)	78 (0.6)
Elementary	2017 (8.2)	905 (7.2)	1112 (9.2)
High school	11,170 (45.4)	5291 (42.4)	5879 (48.6)
Academic	11,263 (45.8)	6232 (49.9)	5031 (41.6)
Physical activity			
Time spent sedentary (% of awake time)	0.54 (0.47, 0.61)	0.52 (0.45, 0.59)	0.56 (0.49, 0.63)
Time spent in moderate or vigorous physical activity (% of awake time)	0.06 (0.04, 0.08)	0.06 (0.04, 0.08)	0.06 (0.04, 0.08)
Audit (n, % with > 2–3 drinks/week)	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	2.0 (0.0, 3.0)
Diabetes (n, %)	1594 (6.3)	585 (4.6)	1009 (8.1)
Fasting glucose (mmol/L)	5.6 (5.2, 6.0)	5.4 (5.1, 5.8)	5.7 (5.4, 6.1)
Blood pressure medication (n, %)	4437 (18.2)	2085 (16.8)	2352 (19.7)
Lipid lowering medication (n, %)	1624 (6.7)	651 (5.3)	973 (8.1)
Systolic blood pressure (mmHg)	124 (114, 136)	121 (110, 134)	127 (118, 138)
Diastolic blood pressure (mmHg)	77 (70, 84)	76 (69, 84)	78 (72, 85)
Cholesterol (mmol/L)	5.5 (4.8, 6.2)	5.6 (5.0 6.3)	5.3 (4.7 6.0)
LDL (mmol/L)	3.40 (2.80, 4.10)	3.40 (2.80, 4.00)	3.40 (2.80, 4.10)
HDL (mmol/L)	1.60 (1.30, 1.90)	1.80 (1.50, 2.10)	1.40 (1.10, 1.60)
Triglycerides (mmol/L)	1.0 (0.8, 1.5)	0.9 (0.7, 1.3)	1.1 (0.8, 1.6)
hs-CRP (mg/L)	1.0 (0.6, 2.1)	1.0 (0.6, 2.2)	1.0 (0.6, 2.0)
Segment involvement score (SIS)			
SIS = 0 (n, %)	14,579 (57.9)	9010 (70.7)	5569 (44.8)
SIS 1–3 (n, %)	7600 (30.2)	3084 (24.2)	4516 (36.3)
SIS ≥4 (n, %)	3001 (11.9)	643 (5.0)	2359 (19.0)

[a] Self-reported weight.
[b] Measured at examination. Median (interquartile range) or proportions (%) are given. DM, diabetes mellitus; SCAPIS, Swedish CArdioPulmonary bioImage Study.

questions and these non-responses were coded as missing values. In association studies, missing predictor values were imputed under fully conditional specification allowing for non-linear associations during imputation and sex interactions. Model parameters were estimated in each of the imputed datasets separately. These estimates and their standard errors were combined using Rubin's rules. Based on the total fraction of missing data, 25 imputations were made. All analyses were made using the freely available statistical software R version 4.01.40 using functions from the rms (regression modelling strategies) and mice (multivariate imputation by chained equations) add-on packages. Detailed code for fitting the CPM and calculating exceedance probabilities is available in [26].

3. Results

3.1. Cohort characteristics

Valid data on SIS and Duke estimates from CCTA and CACS from CT in subjects with no previous myocardial infarction, PCI (percutaneous coronary intervention) or CABG (coronary artery bypass graft) were available for 25,181 and 28,699 individuals respectively. A detailed analysis of exclusions and missing data has been published previously [17]. In the current analysis, due to updates of our registry data, one additional individual was classified as having had a previous myocardial infarction compared to our previous report [17]. Individuals with prevalent CHD, who were excluded, had significantly higher weight at both age 20 and at examination compared with individuals free of previous CHD (weight age 20; 70 [IQR 62 - 75] kg versus 65 [IQR 75 - 76] and weight at examination; 85 [IQR 77 - 97] *versus* 79 [IQR 69 - 89]). The weight gain was also higher in this group (18,4 [IQR 9,9 - 28.3] versus 13.4 [7.0 - 22.1]).

Demographic and clinical characteristics of the study population used for the analysis of the main aim (n = 25,181) are presented in Table 1, while characteristics on the population studied in relation to CACS (n = 28,699) are presented in the Supplemental Table S1. The median age of the population at examination was 57.3 years with an even distribution between men and women (50.6% women). According to their self-report, 0.8% of the men and 0.7% of the women were obese at age 20 (BMI >30 kg/m^2), whereas 20.8% of the men and 19.0% of the women were obese at mid-life examination. The median weight-gain from age 20 until the time of mid-life examination was 13.4 kg (interquartile range, IQR 7.0–22.1) and 94.9% of men and 93.2% of women gained weight. As expected, the distribution of SIS, Duke and CACS was highly skewed (Supplemental Figs. S2-S4). SIS ranged from 0 to 11 in both men and women; 45% of the men, and 71% of the women had a SIS of zero.

Data for all variables were complete for 22,204 (88%) of individuals in the cohort. The proportion of missing values across the 11 variables included in modelling varied between 0 and 7.6%. Individuals who did not report their weight at age 20 (7.6%) were more likely to have missing values for physical activity, education level, alcohol intake and current smoking and were more often women and generally had more

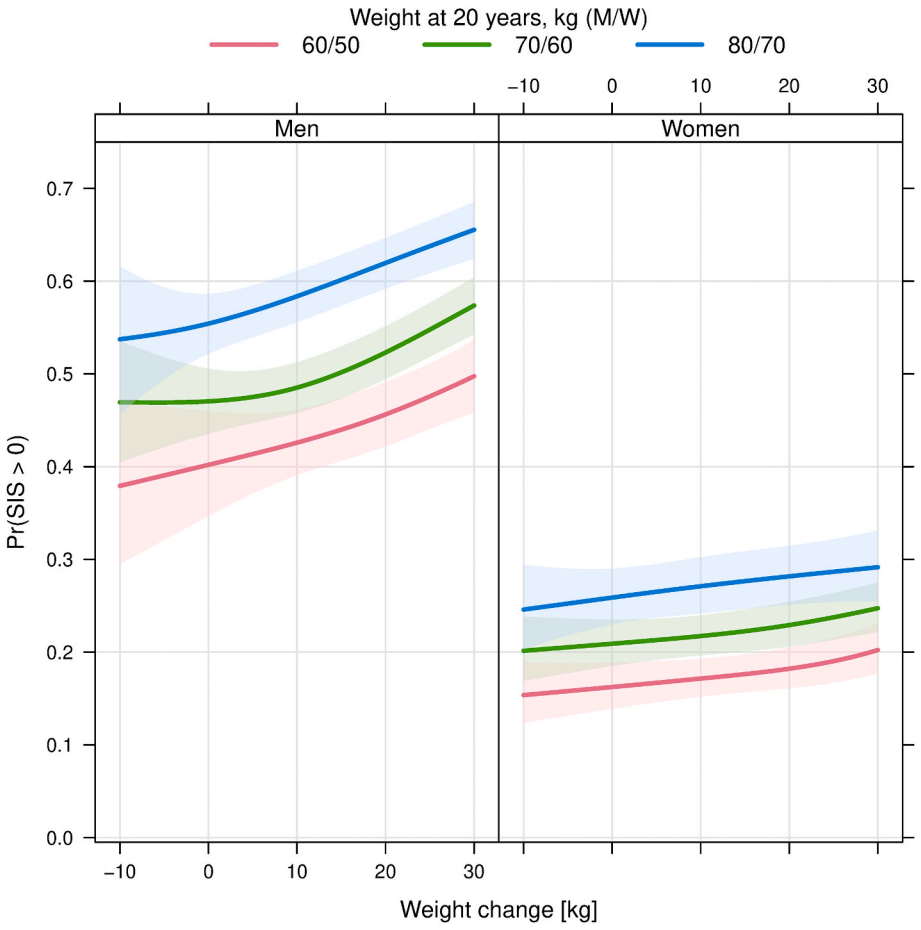

Fig. 1. Probability of having SIS >0 in relation to three different body weights at age 20 and subsequent weight gain until midlife in men and women.
Relationship between weight gain from age 20 to time of investigation and the probability of having higher SIS in SCAPIS participants without established CHD who underwent successful CCTA (n = 25,181). The probability is estimated at three levels of body weight at age 20 in men (60, 70 and 80 kg weight at age 20) and women (50, 60 and 70 kg weight at age 20) separately (the weights represent the approximate sex-specific 10th, 50th and 90th percentiles of self-reported weight). Shaded areas represent the 95% CI. SIS, Segment involvement Score; SCAPIS, Swedish CArdioPulmonary bioImage Study; CHD, coronary heart disease; CCTA, coronary computed tomography angiography.

Table 2
Weight at age 20 and weight at midlife and odds for having higher segment involvement score (SIS).

	Men				Women			
	OR	95% CI lower	95% CI higher	*p*	OR	95% CI lower	95% CI higher	*p*
Higher weight at age 20	1.58	1.31	1.91	<0.001	1.56	1.32	1.85	<0.001
Higher weight in midlife	1.75	1.59	1.91	<0.001	1.54	1.35	1.75	<0.001

The odds ratio (OR) for having higher SIS for a 15 kg higher body weight at age 20 and a 15 kg higher body weight at midlife (body weight increase from age 20 until examination was set to zero). Model adjusted for site, age, height, LDL, smoking, alcohol intake, education level and physical activity (Model 1). CI, confidence interval.

Table 3
Weight gain and odds for having higher segment involvement score (SIS).

	Men					Women				
Weight at age 20 (kg)	OR	95% CI lower	95% CI higher	*p*		Weight at age 20 (kg)	OR	95% CI lower	95% CI higher	*p*
60	1.17	0.95	1.44	0.145		**50**	1.10	0.97	1.26	0.136
70	1.13	1.00	1.28	0.049		**60**	1.08	0.96	1.22	0.189
80	1.21	1.10	1.34	0.000		**70**	1.09	0.97	1.23	0.137

Relationship between weight gain from age 20 to time of investigation and the probability of having higher SIS estimated at three levels of body weight at age 20 in men and women separately. The odds ratio (OR) represents the effect of a 15 kg weight gain (mean weight gain in the sample). Model adjusted for confounders site, age, height, LDL, current smoking, frequency of alcohol intake estimated using AUDIT, attained education level and physical activity measures (Model 1). CI, confidence interval.

cardiovascular risk factors (they were slightly older, heavier and had higher SBP, lower education and more diabetes). Model fit was acceptable, based on visual inspection of the quantile-quantile plot of the probability-scale residuals from the CPM.

3.2. Weight at age 20 and at age 50–64 years are both associated with higher risk of coronary atherosclerosis

Body weight at age 20 was associated with a higher probability of SIS >0 at midlife in both men and women ($p < 0.001$, Fig. 1, Table 2). The association changed only marginally in complete case analysis

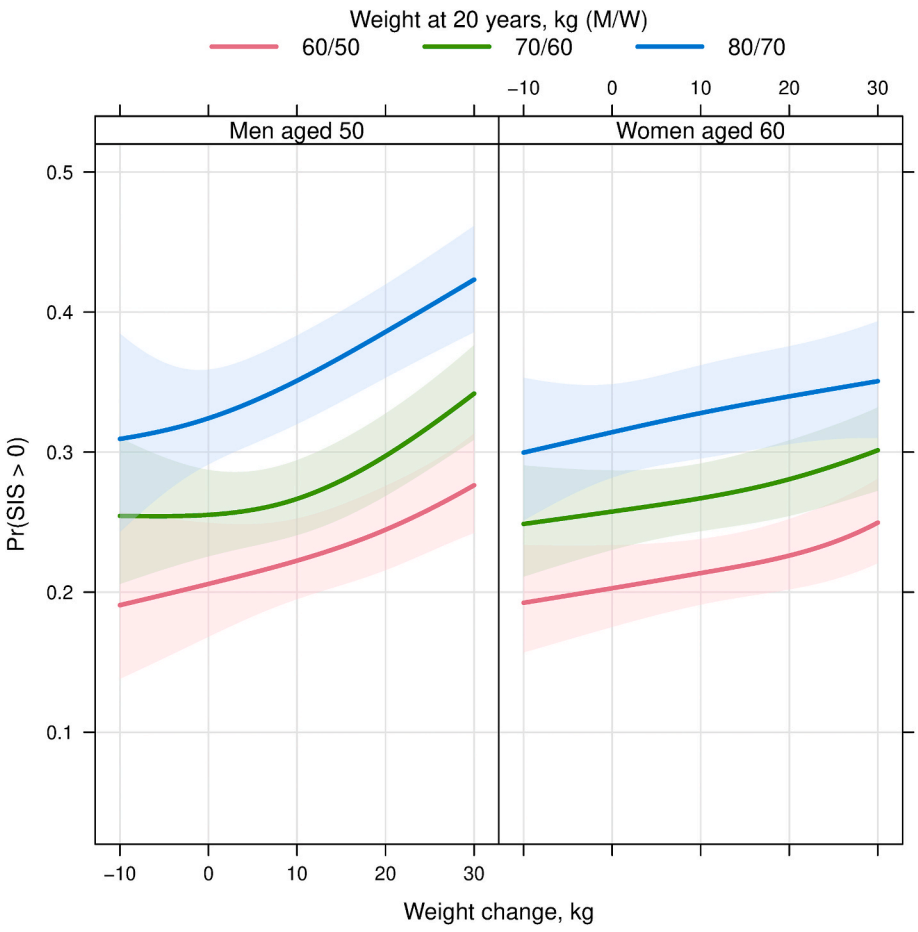

Fig. 2. Probability of having SIS >0 in relation to three different body weights at age 20 and subsequent weight gain until midlife in men aged 50 years and women aged 60 years.
Relationship between weight gain from age 20 to time of investigation and the probability of having higher SIS in SCAPIS participants without established CHD who underwent successful CCTA (n = 25,181). The probability is estimated for a 15 kg weight increase at three levels of starting body weight at age 20 in men (60, 70 and 80 kg weight at age 20) and women (50, 60 and 70 kg weight at age 20) separately (the starting weights represent the approximate sex-specific 10th, 50th and 90th percentiles of self-reported weight).Shaded areas represent the 95% CI; SIS, Segment involvement Score; SCAPIS, Swedish CArdioPulmonary bioImage Study; CHD, coronary heart disease; CCTA, coronary computed tomography angiography.

(Supplemental Table S2) and further adjustments for potential mediators slightly weakened the association that was still significant (OR in men 1.27 (95% CI: 1.04–1.54, Supplemental Table S2) and in women 1.41 (95% CI: 1.18–1.67, Supplemental Table S2). When SIS was exchanged for Duke score or CACS similar associations were found (see Supplemental Tables S3 and S4).

Also, body weight at mid-life examination (age 50–64 years) was associated with higher probability of SIS >0 at mid-life in both men and women ($p < 0.001$, Table 2). The association changed only marginally in complete case analysis (Supplemental Table S5) and was slightly weakened when adjusting for potential mediators but still significant (OR in men 1.50 (95% CI: 1.37–1.65, Supplemental Table S5) and women 1.40 (95% CI: 10 1.23–1.60, Supplemental Table S5). When SIS was exchanged for Duke score or CACS similar associations were found (Supplemental Tables S6 and S7).

3.3. Weight change between age 20 and age 50–64 years is associated with higher risk of coronary atherosclerosis

There was a significant interaction between weight at age 20 and weight at the mid-life examination ($p < 0.001$) on the probability of having SIS >0. When the effect of a weight change of 15 kg from age 20 to the time of mid-life examination was estimated for three levels of body weight at age 20 (approximately the sex-specific 10th, 50th and 90th percentiles), a significant association between weight gain and SIS was seen at the two higher levels of body weight at age 20 for men (Fig. 1, Table 3), but for none of the body weights at age 20 in women (Fig. 1, Table 3). The association was weakened in complete case analysis such that only the highest weight at age 20 in men was significantly associated with higher SIS (Supplemental Table S8). The association was further weakened when adjusting for potential mediators (Supplemental, Table S8). When SIS was exchanged for Duke score or CACS similar pattern of associations were found (Supplemental Figs. S5 and S6, Tables S9 and S10).

Bivariate distributions of self-reported weight at age 20 and weight at examination and their relation to model estimated probability of having SIS >0 and SIS ≥4 are shown in Supplemental Fig. S7 (bivariate associations for Duke score or CACS are shown in Supplemental Figs. S8 and S9).

3.4. The effect of weight change in men and women on atherosclerosis

We did not observe a significant interaction between weight at age 20, weight at mid-life examination and sex (p=0.337). We also tested whether a 15 kg weight increase affects the probability of higher SIS differently in a 50 year old male compared with a 60 year old women of comparable weight and height at age 20 (Fig. 2). The probability of having higher SIS after a 15 kg increase in weight in men at the age of 50 (weight at age 20 = 70 kg, height = 179 cm) was comparable to that of women at the age of 60 years (weight at age 20 = 60 kg, height = 166 cm) with an OR of 1.07 (95% CI: 0.90–1.28). Similar findings were seen when Duke score or CACS were analysed (Supplemental Figs. S10 and S11).

4. Discussion

In this population-based study, our data and statistical model allowed us to carefully dissect the associations between weight at age 20, weight in midlife or weight gain with coronary atherosclerosis. We found that weight at age 20 and weight at midlife were both strongly and

positively associated with the probability of having coronary atherosclerosis regardless of sex. However, weight gain from age 20 until midlife was only modestly associated with coronary atherosclerosis and we found no evidence for a sex-difference in this association when accounting for the later development of coronary atherosclerosis in women.

In this study, subclinical coronary atherosclerosis was both directly visualized in the coronary arteries using CCTA (SIS and Duke score) or measured as coronary calcification score (CACS). These estimates reflect different pathophysiological processes with many similarities, but also several unique properties reflecting different aspects of subclinical atherosclerosis [17,19]. However, the association between body weight and weight change and subclinical coronary atherosclerosis was similar regardless of which outcome was used, suggesting that all these measures reflect similar pathophysiological processes in relation to weight.

The analysis of mid-life body weight confirmed the well-established cross-sectional association between elevated body weight and coronary atherosclerosis [5,27]. It is also well established that being overweight or obese in mid-life translates into an increased risk of developing clinical cardiovascular disease [28,29].

It is also evident in our study that even moderately elevated body weight at age 20 (adjusted for height) is associated with higher probability of coronary atherosclerosis. This corroborates earlier studies, showing that early adulthood overweight and obesity, especially of the abdominal type, is related to coronary calcifications in midlife [27, 30–35]. Given that elevated body weight in a young person, particularly a man, may represent high muscle mass rather than fat, our finding is an important validation of earlier results.

Although not analysed in the current paper, individuals who were excluded from the study due to prevalent CHD had significantly higher weight at age 20, weight at examination and also weight gain, further supporting the importance of body weight for development of coronary artery disease.

4.1. Weight increase

We found a positive association between weight gain and coronary atherosclerosis although not as strong as the association between early adulthood weight and weight at the examination. The association was stronger with increasing weight in early adulthood. There are only a few studies that have addressed this issue, with contrasting results. Surprisingly, in the CARDIA study [15], weight gain after 20 years of follow-up from the first body weight measurement was inversely related to CACS. However, IMT of the carotid arteries were positively associated with weight gain in both the CARDIA study [15] and in the ARIC study [13]. The reason for the discrepant results on CACS between our studies is difficult to explain. However, both initial and follow-up BMI was higher in CARDIA and the subjects in CARDIA were younger at the time of CACS measurement (mean age 45 years) than in the SCAPIS study (mean age 57 years) and were therefore at an earlier phase of atherosclerosis.

4.2. Sex differences

It is well known that cardiovascular disease develops later in women than in men, and we have previously reported that also subclinical atherosclerosis has a 10 year delay in onset in women [17] and that fat mass is more closely related to cardiovascular risk factors in men than in women [38]. The effect of sex on the relation between early adulthood weight and weight gain on subclinical atherosclerosis is not well studied. In the current study the odds ratios associated with body weight (at age 20 and in midlife) for having coronary atherosclerosis were very similar for men and women and we found no significant interaction between sex and body weight in their effect on coronary atherosclerosis. There was an apparent difference between men and women in the effect of weight change on coronary atherosclerosis. However, in additional analyses we compared the effect of weight gain on midlife coronary atherosclerosis at different ages for men and women and found that probabilities of having coronary atherosclerosis were very similar. Interactions with sex have rarely been reported in earlier studies on coronary atherosclerosis. In a large cross-sectional study of >30,000 adult Koreans, obesity was closely related to CACS in both women and men [33]. In a recent meta-analysis on the effect of weight gain on clinical cardiovascular disease, no convincing sex difference could be detected [14]. Furthermore, another meta-analysis showed that higher BMI had the same deleterious effects on risk of incident CHD in women and men [2].

4.3. Confounders and mediators

In the present study, we adjusted for age and some lifestyle factors, such as smoking, education level, exercise habits and alcohol intake that are likely to be confounders in the relationship between obesity and coronary atherosclerosis. Since Mendelian randomization studies show that obesity is causally related to established risk factors such as hypertension, diabetes and HDL cholesterol [39], we regarded those risk factors as mediators in the "obesity → coronary atherosclerosis" relationship and therefore did not include them as confounders in the analysis. In a Mendelian randomization study [39], obesity was not causally related to LDL cholesterol, but since LDL cholesterol is associated with both BMI and atherosclerosis, LDL cholesterol was included as a confounder in the model. Height was also included because taller people are heavier. In a separate model, we also adjusted for the potential mediators; systolic blood pressure, type 2 diabetes, treatment for hyperlipidemia and hypertension. Unfortunately, the design of the study did not allow adjustment for covariates at age 20. We have presented our view on these relationships as a directed acyclic graph (DAG, Supplemental Fig. S1).

4.4. Limitations

A limitation of the current study is that measured body weight at age 20 was not available, so we had to rely on self-reported data. A previous study [40] found the correlation between measured and self-reported body weight at age 20 to be 0.82, which is not perfect, but good enough for large-scale epidemiological studies. In addition, self-reported body weight was not systematically affected by sex, lending further credibility to our findings [40]. Another limitation is the lack of information on relevant covariates at age 20. Also, we acknowledge that we have studied mainly subjects of European descent in one country, and our findings may not be generalizable to other populations. Finally, our study is observational, which limits the ability to infer causal relationships. The major strength of the present study is the sample size of more than 25,000 individuals examined with a common, standardized, and detailed protocol. Since the statistical power of a study ultimately is determined by the hypothesized effect size and the variability in the data, this sample size allowed us to detect all but fairly trivial associations and lower-order interactions. Another strength is that we get similar results using three different measures of atherosclerosis which brings robustness to our findings.

4.5. Future directions

This study has potential clinical implications since most acute coronary events are caused by a large and often ruptured atherosclerotic plaque in the coronary arteries [41]. We show that the risk of having widespread coronary atherosclerosis increases with higher body weight both at age 20 and at age 50-64 years. Together with previous data showing elevated body weight in adolescence to be a strong risk factor for early clinical disease [3,14,37,42], our findings suggest there is a strong case to implement weight control programs both in early life and in adulthood to reduce future risk of incident coronary heart disease. Since Mendelian randomization studies have shown that obesity is

causally related to future coronary events [36,37], and that a high SIS and CACS could predict myocardial infarction [18,21,22], it would be interesting in future studies to use Mendelian randomization to test whether the links between weight at age 20 and later weight gain regarding SIS are additive and causal.

4.6. Conclusion

In both men and women, there was a strong positive association between self-reported weight at age 20 as well as between weight at examination and mid-life coronary atherosclerosis. However, weight increase *per se* from age 20 until mid-life was only modestly associated with coronary atherosclerosis. The association between weight gain and coronary atherosclerosis was mainly seen in men, however, in an analysis adjusting for the 10-year difference in disease development between men and women no significant sex difference on the effect of weight gain could be detected.

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Author contributions

The SCAPIS project follows the ICMJE recommendations for author contributions. All listed authors fulfil these recommendations which includes substantial contribution to the design of the work, the analysis and interpretation of data as well as drafting and critically revising the intellectual content. Finally, all authors approve of the submission and agree to be accountable for all aspects of the work.

Declaration of competing interest

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Appendix A. Supplementary data

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