Genetics and life course epidemiology of cardiometabolic disease: towards personalized medicine

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Part II: CARDIOMETABOLIC AND GENETIC RISK PROFILES OVER THE LIFE COURSE IN DIFFERENT GENERATIONS OF MEN AND WOMEN

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Adverse generational changes in obesity development converge at midlife without increased cardiometabolic risk

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ABSTRACT

Objective: Obesity is becoming a global public health problem, but it is unclear how it impacts different generations over the life course. Here, we performed a descriptive analysis of the age-related changes in anthropometric measures and related cardiometabolic risk factors across different generations.

Methods: We studied the development of anthropometric measures and related cardiometabolic risk factors during 26 years of follow-up in the Doetinchem cohort (n=6314 at baseline). All analyses were stratified by sex and generation, *i.e.* 10-year age groups (20–29, 30–39, 40–49, and 50–59 years) at baseline. We used generalized estimating equations to test for generational differences.

Results: Weight, BMI, waist circumference, and prevalence of overweight and obesity were in general higher in the younger generations during the first 10-15 years of follow-up. From age 50–59 years onwards, these measures converged in all generations of men and women. Among cardiometabolic risk factors, only type 2 diabetes showed an unfavorable shift between the two oldest generations of men.

Conclusions: We observed that compared to the older generations, the younger generations had obesity at an earlier age, but did not reach higher levels at midlife and beyond. This increased exposure to obesity was not (yet) associated with increased prevalence of cardiometabolic risk factors.

INTRODUCTION

The prevalence of obesity has increased dramatically over the last decades, and it is estimated that by 2030 more than one billion people will have obesity.[1] This poses a global public health problem as obesity is strongly associated with cardiometabolic risk factors and diseases, such as hypertension, hypercholesterolemia, insulin resistance, type 2 diabetes (T2D) and cardiovascular disease (CVD),[2-5] all of which are associated with morbidity and reduced life expectancy.[6]

Obesity prevalence increases with age, with more progressive changes taking place from 20 to 60 years.[7,8] This upward trend follows a sex-specific course, with men reaching a body mass index (BMI) plateau at a younger age than women.[9] In addition to age and sex, obesity differs by birth cohort, which are defined as groups of people born in the same period of time.[10] Individuals belonging to a particular birth cohort are likely to share a cumulative set of experiences that may be different from those born earlier or later.[11] For instance, the oldest generations in their younger years were exposed to a less obesogenic food environment and a less sedentary life style than more recent generations.[12] The extent of exposure to such obesity-promoting environments and consequently to obesity affects development of obesity-related conditions: a longer exposure to obesity has been associated with higher risk of T2D [13,14] and CVD.[15] Altogether, both timing and duration of obesity are important in the development of cardiometabolic disease. Therefore, a more comprehensive evaluation of the development of obesity prevalence and its long-term effects on associated cardiometabolic risk factors is important.

We have previously studied the development of overweight and obesity during 16 years of follow-up in a Dutch population of men and women aged 20-59 at baseline, where we showed an unfavorable increase of overweight and obesity in the most recently born generations compared to the older ones.[8] However, at the end of the 16-year follow-up the most recently born generations had barely reached midlife, which is typically a period that predates the manifestation of cardiometabolic disease and is a strategic window for early detection and prevention of CVD. Therefore, our previous study could not adequately assess trends of obesity and related cardiometabolic factors beyond midlife in the most recently born generations.[16] Another limitation of our previous study was that it used only BMI as a measurement of overweight and obesity. However, BMI measurements alone are insufficient to assess visceral obesity, thus failing to fully capture cardiometabolic risk. Recent studies emphasize the importance of using in addition to BMI waist circumference, as an important measure of visceral obesity, to better assess and predict obesity and

cardiometabolic risk.[17] Therefore, in the current analyses, we further assessed the development of obesity and related cardiometabolic risk factors in the same population by including data from more recent measurements, extending the follow-up period by 10 years to a total of 26 years and also assessing waist circumference. Our aim was to perform descriptive analyses of the changes in anthropometric measures and related cardiometabolic risk factors over the life course, by sex and generation.

METHODS

Population

The Doetinchem Cohort Study (DCS) is a prospective population-based cohort study including 7769 men and women aged 20-59 years at baseline living in Doetinchem, predominantly from Dutch Caucasian descent, between in 1987-1991 (round 1). Participants of the first round were invited for follow-up examinations every 5 years. The response rates varied between 75% and 80% in all rounds. The study design of DCS has previously been described in more detail. [18,19] For the present analyses, we included participants who took part in at least two rounds (n=6391) and excluded pregnant women only for that specific round (round 1-6: respectively 77, 43, 18, 3, 1, 1). This resulted in a total of 6314, 6069, 4897, 4516, 4015 and 3437 participants in round 1, 2, 3, 4, 5 and 6 respectively. This selection process is described in a participant flowchart (Figure 1). All participants gave written informed consent and the study was approved according to the guidelines of the Helsinki Declaration by the external Medical Ethics Committee of the University Medical Center Utrecht (UMCU).

Measures

Demographic characteristics, medical history of chronic diseases, medication use, and lifestyle factors were collected using standardized questionnaires. Trained staff performed standardized measurements of anthropometric traits (height, weight, waist circumference), blood pressure and blood sampling during a visit to the municipal health service. Detailed description of these measures has been reported elsewhere.[8] Overweight was defined as a BMI between 25-30 kg/m2, and obesity as a BMI equal or greater than 30 kg/m2. The mean value of two blood pressure measurements was used in the analyses. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg, and/or diastolic blood pressure (DBP) ≥ 90 mmHg, and/or use of antihypertensive medication (according to World Health Organization definition).[20] Total and HDL cholesterol were measured until 1998 in non-fasting EDTA-plasma and from 1998 onwards in serum at the Lipid Reference

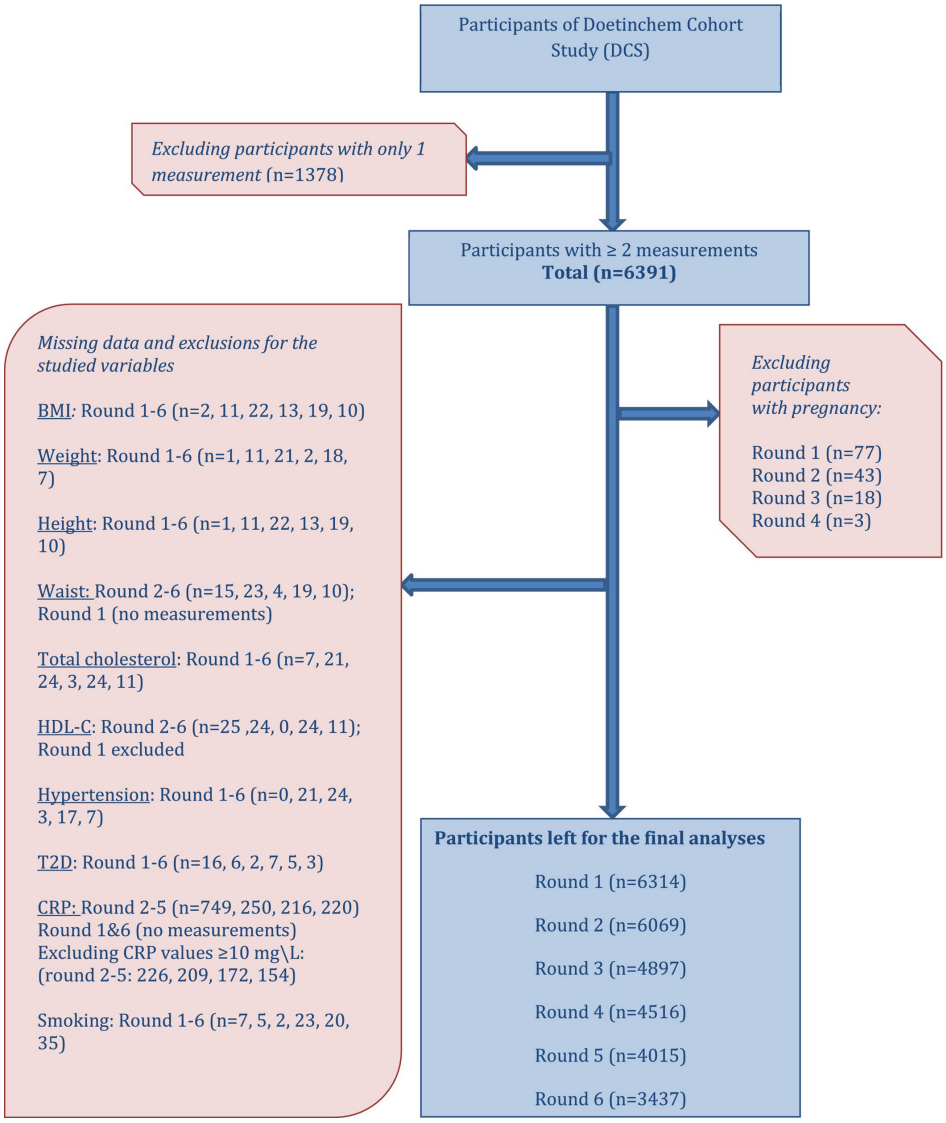

Figure 1. Flowchart of study participant selection. CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; T2D, type 2 diabetes

Laboratory (LRL), using standardized enzymatic methods. Hypercholesterolaemia was defined as total cholesterol 6.5 mmol/l and/or use of cholesterol-lowering medication and low high-density lipoprotein cholesterol (HDL-C) was defined based on the NCEP-ATPIII definition of cardiometabolic syndrome as HDL-C < 1.03 mmol/l and < 1.29 mmol/l in men and women, respectively.[21] For CRP, standardized enzymatic methods were used to retrospectively determine CRP in four rounds (R2-R5) using blood plasma that had been stored in freezers. This examination of all avail-

able samples from consecutive rounds (R2-R5) in one assay run was performed to reduce the chance of measurement error and batch effects.

T2D cases were defined on basis of self-report or level of random glucose (> 11.1 mmol/l). Most self-reported diabetes cases were verified with information from the general practitioner or pharmacist (86%). The highest level of completed education during follow-up was classified into three categories: low (intermediate secondary education or less), intermediate (intermediate vocational or higher secondary education), and high (higher vocational education or university). Smoking was assessed by means of a questionnaire, and categorized in current, ex- and never smokers.

Statistical Analyses

The development in the prevalence of anthropometric measures and cardiometabolic risk factors over time in four 10-year generations were described. The generations were defined on the baseline age of the participants: 20–29, 30–39, 40–49, and 50–59 years, further referred to as those who were in their 20s, 30s, 40s, and 50s, respectively. The prevalence or mean (median for non-normally distributed variables of anthropometric measures and cardiometabolic risk factors was plotted against the mean age of these generations at the time of measurement, for men and women, separately. A generation shift occurs when the difference in the prevalence or mean of a particular measure of obesity or cardiometabolic risk factor between generations at similar age is significantly different, as determined by logistic regression for dichotomous outcomes and linear regression for continuous outcomes. To take the correlations amongst repeated observations on the same participants into account, we used generalized estimating equations (GEE) with auto-regressive structure similar to Hulsegge et al.[8] In order to distinguish between differences in earlier and later lifetime points, we performed the analyses separately for earlier development (round 1, 2, 3 and 4) and later development (round 3, 4, 5 and 6) and then for the time development over the total period, comprising for all six rounds. At round 3, 4, 5 and 6 the mean age of a generation was approximately the same as the mean age of a generation born 10 years earlier at round 1, 2, 3 and 4, respectively. Therefore, for the earlier development, measures of obesity and cardiometabolic risk factors at round 3 and 4 of a generation were compared to those of a generation born 10 years earlier at round 1, 2, respectively. In the later development, round 5 and 6 of a generation were compared to the generation born 10 years earlier at round 3 and 4, respectively. Finally, for the time development over the total period, the data at round 3, 4, 5 and 6 of a generation were compared with those of a generations born 10 years earlier at round 1, 2, 3 and 4, respectively. As waist circumference was not measured in round 1, GEE was performed comparing round 4,

5 and 6 (total period), 4 and 5 (earlier development) and 5 and 6 (later development) of a generation with round 2, 3 and 4 (total period), 2 and 3 (early development) and 3 and 4 (later development), respectively, of a 10-year older generation. As the HDL-C values in the first round deviated markedly from the values in the other rounds, these data were omitted in the current analyses and therefore GEE for HLD-C was performed comparing the same rounds as for waist circumference. C-reactive protein (CRP) was not measured in round 1 and 6, and therefore only round 4 and 5 of a generation were compared with round 2 and 3 of a 10 year-older generation.

The analyses were adjusted for age and a p-value < 0.05 was considered statistically significant. Descriptive analyses were performed in SPSS Statistics 23 and GEE analyses in SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Population characteristics

The general characteristics of the study population at baseline are presented in Table 1. In the total population, the mean age was 40.5 years and 48% were men. Participants in the older generations had a lower educational level, a lower percentage of current smokers but a higher percentage were former smokers compared to the younger generations. The oldest generation of women had the highest percentage of never smokers and the lowest of current smokers. Participants in the older generations had more unfavourable baseline levels of SBP, DBP and total cholesterol and more often used antihypertensive and cholesterol-lowering medication. Women in the younger generations entered the menarche earlier. The oldest generation of women (50-59 years at baseline) had the highest number of children (n = 2.9) compared to the other three generations (n = 2.1).

Anthropometric measures

Figure 1 shows the development of anthropometric measures and BMI as well as the prevalence of overweight and obesity. Weight increased whereas height decreased with age in both men and women in all generations, and were both significantly higher in the younger generations (p-value < 0.001) when compared at a similar age with participants born 10 years earlier (Figure 1(a-d), Table 2.1 & Table 2.2). BMI, waist circumference, prevalence of overweight and obesity increased with age in all generations, and were in general significantly higher in the younger generations compared to the older generations (Figure 1 (e-i), Table 2.1 & Table 2.2). Among men, such unfavourable generation shifts in the aforementioned traits were present

Table 1. General baseline characteristics for four generations in the Doetinchem Cohort Study (N=6314)

		20-29 years		30-39 years		40-49 years		50-59 years	
	Total (N= 6314)	**Men** (N=469)	**Women** (N=589)	**Men** (N=941)	**Women** (N=1040)	**Men** (N=928)	**Women** (N=955)	**Men** (N=659)	**Women** (N=733)
Baseline Age (years)	40.0 ± 10.2	25.4 ± 2.9	25.3 ± 2.8	35.1 ± 2.9	35.0 ± 2.7	44.3 ± 2.6	44.2 ± 2.8	54.5 ± 2.8	54.6 ± 2.9
Education (%)									
Low	63	52	49	49	65	59	76	61	83
Intermediate	21	37	41	27	19	21	12	17	9
High	16	11	10	23	16	21	13	22	8
Smoking (%)									
Current smokers	35	39	40	37	38	34	33	31	25
Former-smokers	29	13	17	30	31	39	25	46	19
Non smokers	37	48	44	33	31	28	42	23	57
BMI (kg/m2)	24.6 ± 3.5	23.4 ± 2.8	22.6 ± 3.4	24.5 ± 2.9	23.5 ± 3.5	25.6 ± 3.0	24.6 ± 3.6	26.0 ± 3.0	26.3 ± 4.0
SBP (mmHg)	122 ± 15	125 ± 12	114 ± 11	124 ± 12	113 ± 12	125 ± 14	118 ± 15	130 ± 16	126 ± 16
DBP (mmHg)	78 ± 10	74 ± 9	72 ± 9	78 ± 10	73 ± 9	81 ± 10	77 ± 10	82 ± 11	80 ± 11
Antihypertenisve medication (%)	19	3	3	8	7	12	16	33	43
Total cholesterol (mmol/l)	5.47 ± 1.08	4.79 ± 0.90	4.95 ± 0.86	5.41 ± 1.06	5.04 ± 0.91	5.84 ± 1.09	5.43 ± 0.94	5.98 ± 0.96	6.18 ± 1.04
HDL-C (mmol/l)[a]	1.25 ± 0.31	1.13 ± 0.24	1.36 ± 0.29	1.12 ± 0.26	1.35 ± 0.30	1.12 ± 0.27	1.39 ± 0.32	1.09 ± 0.26	1.35 ± 0.32
Cholesterol-lowering medication (%)	2	0	0	0	0	2	0	2	4
Female specific									
Age at menarch	13.4 ± 1.5	-	13.1 ± 1.5	-	13.2 ± 1.4	-	13.5 ± 1.5	-	13.7 ± 1.7
Number of children[b]	2.4 ± 1.0	-	2.1 ± 0.9	-	2.2 ± 0.9	-	2.2 ± 0.8	-	2.9 ± 1.4

Values are mean ± SD or %; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure
All data is from baseline (round 1), unless otherwise specified. [a]These are data from round 2 due to a marked deviation of HDL-C values in round 1. [b]Number of children is given as the maximum value of the available rounds.

between all consecutive generations when they were compared over the life course and especially with respect to earlier development, but not to later development. For example, at an average age of 35 years, the obesity prevalence was 8.6% (round 3) in men who were in their 20s at baseline and 4.0% (round 1) in men who were born 10 years earlier (those in their 30s at baseline) (Table 2.1). However, as also seen in Figure 1, BMI, waist circumference and obesity prevalence in the younger generations did not reach significantly higher levels in later life than in the older generations ($p > 0.05$). For example, at the average age of 50 years, the obesity prevalence was 14.6% (round 6) in men who were in their 20s at baseline and 13.9% (round 4) in men who were born 10 years earlier (those in their 30s at baseline). Among women, initially unfavourable, but ultimately converging generation shifts were evident for the three youngest generations. However, the oldest generation of women showed already within the first three rounds elevated levels for BMI, weight, waist circumference, overweight and obesity prevalence compared to the younger three generations. The youngest generation of women (those in their 20s at baseline) had the most unfavorable shift in obesity development, where the prevalence of obesity almost doubled when they reached a similar age compared to those who were in their 30s at baseline (p-value < 0.001).

Cardiometabolic risk factors

Levels of cardiometabolic risk factors increased with age during the 26-year follow-up in all generations of men and women, except for low HDL-C (Figure 2). Hypertension and hypercholesterolemia were more prevalent in men before age 50 than in women. After age 50, hypercholesterolemia was more prevalent in women. However, hypertension and hypercholesterolemia did not differ across the generations, except for the youngest generation of women, who started with a significantly higher prevalence of hypertension compared to those born 10 years earlier ($p = 0.013$) (Figure 2, Table 2.2). In addition, an unfavorable generation shift ($p = 0.042$) was observed in the later development for hypercholesterolemia in men who were in their 30s at baseline compared to those in their 40s at baseline (Figure 1, Table 2.1). Interestingly, the percentage of low HDL-C was significantly lower in the younger generations, resulting in favorable generation shifts particularly in women. Overall, T2D development did not differ across the generations. An unfavorable generation shift for T2D was only observed when comparing the development in men who were in their 50s at baseline with those born 10 years earlier ($p = 0.007$). However, CRP showed a favorable generation shift between men in their 30s at baseline and those in their 40s (p-value=0.018) and between the two oldest generations of men and women (p-value=0.009 and p-value=0.003, respectively). Since CRP is strongly associated with smoking, we assessed smoking prevalence during the follow-up of our

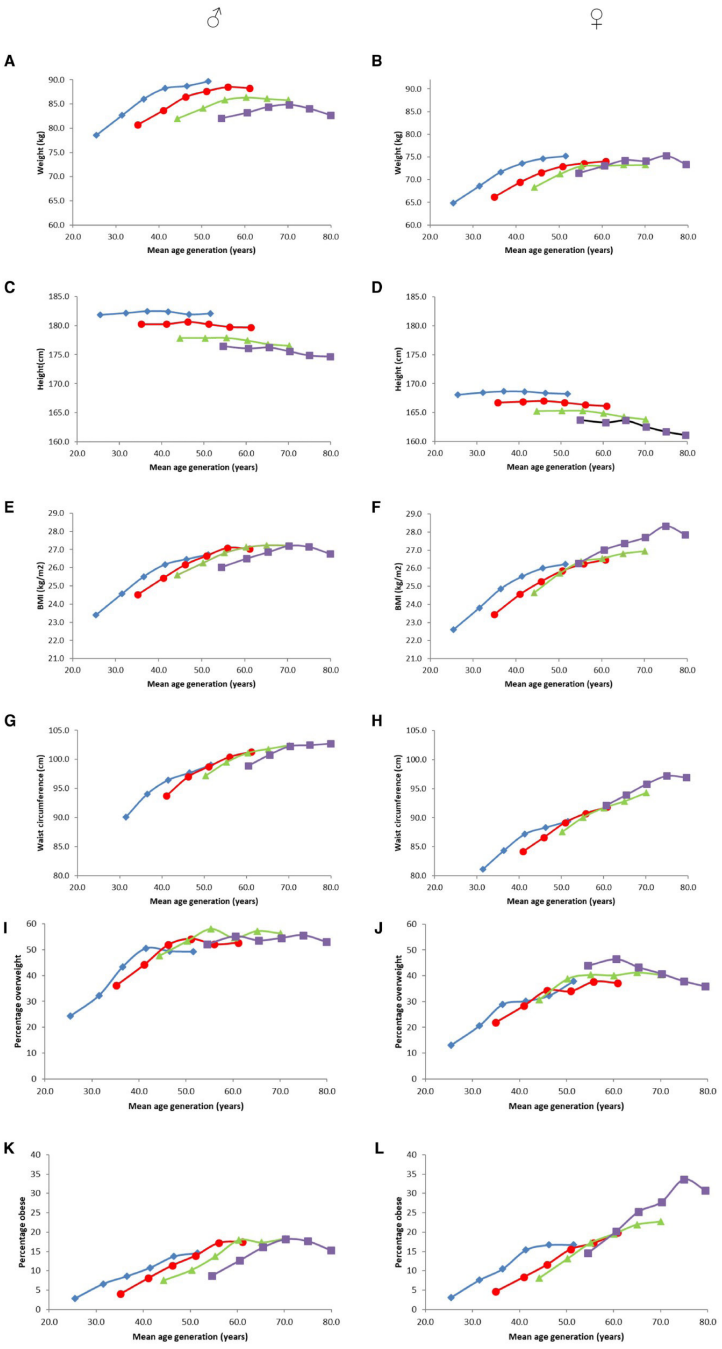

Figure 2. Age-specific mean (SD) or prevalence of anthropometric measures over 26 years follow-up (6 rounds) in those who were in their 20s (20-29; -♦-(blue)), 30s (30-39; -●-(red)), 40s (40-49; -▲-(green)), and 50s (50-59; -■-(purple)) at baseline, stratified by sex: weight (A,B), height (C,D), BMI (E,F), waist circumference (G,H), overweight (25 ≤ BMI < 30 kg/m2) (I,J), obesity (BMI ≥ 30 kg/m2) (K,L).

Table 2.1. Comparison of anthropometric measures and cardiometabolic risk factors over six rounds between consecutive generations in men

	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	p-value[a]	p-value[b]	p-value[c]
Weight (kg)									
20-29	78.5 ± 11.0	82.6 ± 12.0	86.0 ± 12.5	88.2 ± 13.7	88.7 ± 13.7	89.7 ± 14.1	<0.001	0.013	<0.001
30-39	80.7 ± 10.6	83.7 ± 11.2	86.4 ± 11.5	87.6 ± 12.0	88.5 ± 12.4	88.3 ± 12.3	<0.001	<0.001	<0.001
40-49	82.0 ± 10.6	84.1 ± 11.3	85.8 ± 11.7	86.3 ± 11.8	86.1 ± 11.3	85.8 ± 11.8	<0.001	0.03	<0.001
50-59	82.1 ± 10.1	83.2 ± 10.5	84.4 ± 10.9	84.8 ± 11.0	84.1 ± 11.0	82.7 ± 11.4	-	-	-
Height (cm)									
20-29	181.8 ± 6.7	182.1 ± 6.6	182.4 ± 6.9	182.4 ± 6.4	181.9 ± 6.2	182.0 ± 6.2	<0.001	<0.001	<0.001
30-39	180.2 ± 6.5	180.3 ± 6.5	180.7 ± 6.6	180.2 ± 6.4	179.8 ± 6.3	179.7 ± 6.3	<0.001	<0.001	<0.001
40-49	177.8 ± 6.3	177.8 ± 6.3	177.8 ± 6.3	177.4 ±6.0	176.8 ± 6.0	176.5 ± 6.2	<0.001	0.055	<0.001
50-59	176.5 ± 6.5	176.1 ± 6.5	176.3 ± 6.5	175.6 ± 6.2	174.9 ± 6.3	174.7 ± 6.5	-	-	-
Body Mass Index (kg/m2)									
20-29	23.4 ± 2.8	24.6 ± 3.1	25.5 ± 3.2	26.2 ± 3.6	26.5 ± 3.7	26.7 ± 3.8	<0.001	0.39	0.013
30-39	24.5 ± 2.9	25.4 ± 3.1	26.2 ± 3.2	26.6 ± 3.3	27.1 ± 3.6	27.0 ± 3.5	0.033	0.71	0.13
40-49	25.6 ± 3.0	26.3 ± 3.2	26.8 ± 3.4	27.1 ± 3.5	27.2 ± 3.5	27.2 ± 3.6	<0.001	0.23	0.001
50-59	26.0 ± 2.9	26.5 ± 3.1	26.9 ± 3.3	27.2 ± 3.4	27.2 ± 3.3	26.8 ± 3.4	-	-	-
Waist circumference (cm)[d]									
20-29	-	90.1 ± 9.2	94.1 ± 9.3	96.5 ± 10.2	97.7 ± 10.7	99.1 ± 11.4	0.0048	0.48	0.015
30-39	-	93.8 ± 8.9	97.0 ± 9.1	98.9 ± 9.4	100.4± 10.0	101.3 ± 10.0	0.039	0.54	0.11
40-49	-	97.2 ± 9.3	99.5 ± 9.9	101.1 ± 101	101.8 ± 10.0	102.4 ± 10.7	<0.001	0.26	0.005
50-59	-	98.9 ± 9.0	100.8 ± 9.6	102.3 ± 9.8	102.5 ± 9.7	102.7 ± 10.3	-	-	-
Overweight (%)									
20-29	24.4	32.3	43.4	50.6	49.5	49.3	0.0033	0.29	0.008
30-39	36.2	44.2	51.9	54.2	52.1	52.7	0.65	0.096	0.29
40-49	47.7	53.4	58.0	54.6	57.2	56.3	0.25	0.29	0.23
50-59	52.1	55.2	53.6	54.5	55.6	53	-	-	-

Table 2.1. Comparison of anthropometric measures and cardiometabolic risk factors over six rounds between consecutive generations in men (continued)

	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	p-value[a]	p-value[b]	p-value[c]
Obesity (%)									
20-29	2.8	6.6	8.6	10.8	13.7	14.6	0.043	0.53	0.01
30-39	4.0	8.1	11.4	13.9	17.2	17.5	0.021	0.55	0.006
40-49	7.5	10.2	13.7	17.9	17.3	18.3	0.0013	0.80	<0.001
50-59	8.7	12.7	16.1	18.2	17.7	15.3	-	-	-
Hypertension (%)									
20-29	14.3	15.0	19.9	21.2	28.6	32.0	0.76	0.11	0.28
30-39	17.9	23.1	33.3	35.2	44.7	51.1	0.083	0.86	0.30
40-49	23.8	34.9	42.8	51.5	61.6	63.9	0.093	0.71	0.16
50-59	35.4	51.0	59.2	66.2	70.5	70.4	-	-	-
Hypercholesterol-emia (%)									
20-29	3.8	6.8	14.6	14.0	22.1	25.2	0.32	0.58	0.23
30-39	15.0	16.2	24.1	25.9	33.2	35.4	0.11	0.042	0.35
40-49	23.7	20.6	29.6	28.9	33.8	38.4	0.10	0.079	0.33
50-59	29.4	22.8	31.3	32.0	42.5	48.1	-	-	-
Low HDL-C (%)[d]									
20-29	-	25.7	30.9	27.6	29.9	21.8	0.52	0.35	0.23
30-39	-	30.2	30.2	27.3	27.7	25.3	0.14	0.54	0.37
40-49	-	30.4	31.5	25.5	25.1	23.8	0.01	0.089	0.07
50-59	-	30.6	31.5	24.4	24.5	23.6	-		-
Type 2 Diabetes (%)	0.6	0.9	1.1	0.9	2.2	3.1	0.07	0.34	0.13
20-29	0.1	0.4	0.7	2.3	4.3	5.6	0.55	0.96	0.63
30-39	0.9	2.2	3.2	5.5	8.9	10.0	0.0073	0.22	0.11
40-49	1.2	3.2	6.4	9.2	14.4	13.9	-	-	-
50-59									

Table 2.1. Comparison of anthropometric measures and cardiometabolic risk factors over six rounds between consecutive generations in men (continued)

	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	p-value[a]	p-value[b]	p-value[c]
C-Reactive Protein (mg/l)[e]									
20-29	-	0.60 (0.86)	0.72 (1.03)	0.88 (1.24)	0.90 (1.44)	-	-	-	0.72
30-39	-	0.81 (1.17)	0.94 (1.29)	1.02 (1.33)	1.07 (1.61)	-	-	-	0.018
40-49	-	1.10 (1.59)	1.10 (1.70)	1.22 (1.72)	1.20 (1.69)	-	-	-	0.009
50-59	-	1.36 (2.16)	1.43 (2.07)	1.41 (2.03)	1.44 (2.13)	-	-	-	-

Values are mean ± SD, median (interquartile range) or %; Logistic and linear regression using generalized estimating equations, adjusted for age, were used to test whether a generation was, at a similar age, statistically significant different compared to the consecutive generations born 10 years earlier. Logistic and linear regression using generalized estimating equations, adjusted for age, were used to test whether a generation was, at a similar age, statistically significant different compared to the consecutive generations born 10 years earlier. The coloured rectangles and the arrows in the first rows exemplify the comparisons performed for the corresponding p-values. [a]For the earlier development, the difference in all indicated outcomes, except waist circumference, low HDL-C and C-reactive protein, at round 3 and 4 of a generation was compared to the generation born 10 years earlier at round 1, 2, respectively (blue). [b]For the later development, round 5 and 6 of a generation were compared to the generation born 10 years earlier at round 3, 4, respectively (red). [c]Finally, for the time development over the total period, the data at round 3, 4, 5 and 6 of a generation were compared with those of a generations born 10 years earlier at round 1, 2, 3 and 4, respectively (green). [d]Round 4,5 and 6 (whole development), 4 and 5 (earlier development) and 5 and 6 (later development) were compared to round 2,3 and 4 (whole development), 2 and 3 (earlier development) and 3 and 4 (later development), respectively, of a 10-year older generation using linear regression (waist circumference) and logistic regression (low HDL-C). [e]Round 4 and 5 were compared to round 2 and 3 of a 10-year older generation using linear regression. Consecutive generations had approximately a similar age at those moments.

Table 2.2. Comparison of anthropometric measures and cardiometabolic risk factors over six rounds between consecutive generations in women

	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	p-value[a]	p-value[b]	p-value[c]
Weight (kg)									
20-29	64.9 ± 10.3	68.6 ± 11.8	71.7 ± 12.1	73.6 ± 13.6	74.7 ± 13.7	75.2 ± 13.6	<0.001	<0.001	<0.001
30-39	66.2 ± 10.2	69.4 ± 11.4	71.5 ± 12. 1	72.9 ± 12.7	73.6 ± 13.1	74.0 ± 13.3	<0.001	0.42	0.003
40-49	68.3 ± 10.4	71.2 ± 11.7	73.0 ± 12.4	73.1 ± 12.5	73.2 ± 12.0	73.3 ± 12.8	0.096	0.25	0.46
50-59	71.5 ± 11.4	73.1 ± 11.4	74.3 ± 12.4	74.1 ± 13.4	75.2 ± 15.0	73.4 ± 14.0	-	-	-
Height (cm)									
20-29	168.1 ± 6.6	168.5 ± 6.6	168.6 ± 6.6	168.6 ± 6.4	168.4 ± 6.5	168.2 ± 6.4	<0.001	<0.001	<0.001
30-39	166.7 ± 6.0	166.9 ± 6.0	167.0 ± 6.0	166.7 ± 6.1	166.3 ± 6.1	166.1 ± 6.0	<0.001	<0.001	<0.001
40-49	165.3 ± 5.9	165.3 ± 6.0	165.3 ± 5.8	164.9 ± 5.8	164.3 ± 5.7	163.8 ± 5.9	<0.001	0.0046	<0.001
50-59	163.8 ± 6.1	163.3 ± 6.1	163.6 ± 6.0	162.6 ± 6.1	161.7 ± 6.2	161.1 ± 6.0	-	-	-
Body Mass Index (kg/m2)									
20-29	22.6 ± 3.4	23.8 ± 3.9	24.9 ± 4.1	25.5 ± 4.7	26.0 ± 4.8	26.2 ± 4.8	<0.001	0.026	<0.001
30-39	23.5 ± 3.5	24.6 ± 4.0	25.3 ± 4.1	25.9 ± 4.4	26.2 ± 4.6	26.5 ± 4.7	0.20	0.35	0.65
40-49	24.6 ± 3.6	25.7 ± 4.1	26.4 ± 4.4	26.5 ± 4.5	26.8 ± 4.5	26.9 ± 4.6	0.68	0.017	0.20
50-59	26.3 ± 4.0	27.0 ± 4.3	27.4 ± 4.4	27.7 ± 4.9	28.3 ± 5.4	27.9 ± 5.0	-	-	-
Waist circum-ference (cm)[d]									
20-29	-	81.2 ± 10.3	84.4 ± 10.5	87.2 ± 11.6	88.3 ± 2.2	89.3 ± 11.9	<0.001	0.18	0.008
30-39	-	84.2 ± 10.5	86.6 ± 10.8	89.1 ± 11.0	90.7 ± 11.4	91.8 ± 12.3	0.057	0.84	0.24
40-49	-	87.6 ± 10.5	90.1 ± 11.0	91.7 ± 11.1	92.8 ± 11.2	94.3 ± 12.0	0.25	0.065	0.15
50-59	-	92.1 ± 11.4	93.9 ± 11.6	95.8 ± 12.0	97.2 ± 12.8	96.9 ± 12.4	-	-	-
Overweight (%)									
20-29	13.1	20.6	28.9	30.2	32.3	37.9	0.054	0.83	0.012
30-39	21.8	28.3	34.3	34.0	37.7	37.2	0.38	0.31	0.82
40-49	30.7	38.7	40.3	40.1	41.2	40.3	0.016	0.49	0.069
50-59	43.9	46.4	43.3	40.8	37.9	35.9	-	-	-

Table 2.2. Comparison of anthropometric measures and cardiometabolic risk factors over six rounds between consecutive generations in women (continued)

	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	p-value[a]	p-value[b]	p-value[c]
Obesity (%)									
20-29	3.1	7.6	10.5	15.4	16.7	16.7	<0.001	0.071	<0.001
30-39	4.6	8.4	11.6	15.6	17.2	19.9	0.10	0.55	0.007
40-49	8.1	13.1	17.2	19.5	21.9	22.7	0.31	0.089	0.18
50-59	14.6	20.2	25.3	27.8	33.6	30.8	-	-	-
Hypertension									
(%)	4.6	7.6	11.8	16.1	22.7	27.6	0.013	0.79	0.36
20-29	6.3	12.8	23.2	27.2	36.0	38.5	0.45	0.011	0.38
30-39	16.1	27.9	38.1	44.8	54.3	57.1	0.07	0.42	0.48
40-49	31.8	44.4	54.6	60.6	71.4	72.4	-	-	-
50-59									
Hypercholes-	4.6	3.2	6.7	8.0	11.0	16.7	0.98	0.017	0.025
terolemia (%)	7.0	7.5	13.2	20.9	34.6	42.9	0.45	0.22	0.75
20-29	13.4	17.4	34.2	36.8	51.9	52.3	0.85	0.078	0.54
30-39	34.7	37.4	47.0	47.0	54.5	51.0	-	-	-
40-49									
50-59									
Low HDL-C									
(%)[d]	-	28.7	31.8	23.2	25.4	26.0	0.092	0.63	0.95
20-29	-	26.7	28.7	20.6	21.2	19.5	0.0048	0.014	0.008
30-39	-	24.9	26.9	23.7	25.0	23.7	<0.001	0.003	<0.001
40-49	-	32.8	33.5	28.3	29.4	25.4	-	-	-
50-59									

Table 2.2. Comparison of anthropometric measures and cardiometabolic risk factors over six rounds between consecutive generations in women (continued)

	Round 1	Round 2	Round 3	Round 4	Round 5	Round 6	p-value[a]	p-value[b]	p-value[c]
Type 2 Diabetes (%)	0.2	0.0	0.0	0.4	0.7	1.9	0.15	0.85	0.80
20-29	0.3	1.2	0.8	2.0	4.0	4.9	0.81	0.45	0.81
30-39	0.7	1.6	2.0	4.2	6.4	9.7	0.30	0.90	0.65
40-49	1.6	3.5	5.5	10.7	15.3	16.3	-	-	-
50-59									
C-Reactive Protein (mg/l)[e]	-	1.35 (2.35)	1.33 (2.56)	1.20 (2.38)	1.16 (2.11)	-	-	-	0.061
20-29	-	0.97 (1.83)	1.20 (2.10)	1.15 (1.75)	1.07 (1.57)	-	-	-	0.16
30-39	-	1.07 (1.69)	1.21 (1.94)	1.23 (1.84)	1.25 (1.76)	-	-	-	0.003
40-49	-	1.44 (2.06)	1.65 (2.27)	1.60 (2.32)	1.40 (1.93)	-	-	-	-
50-59									

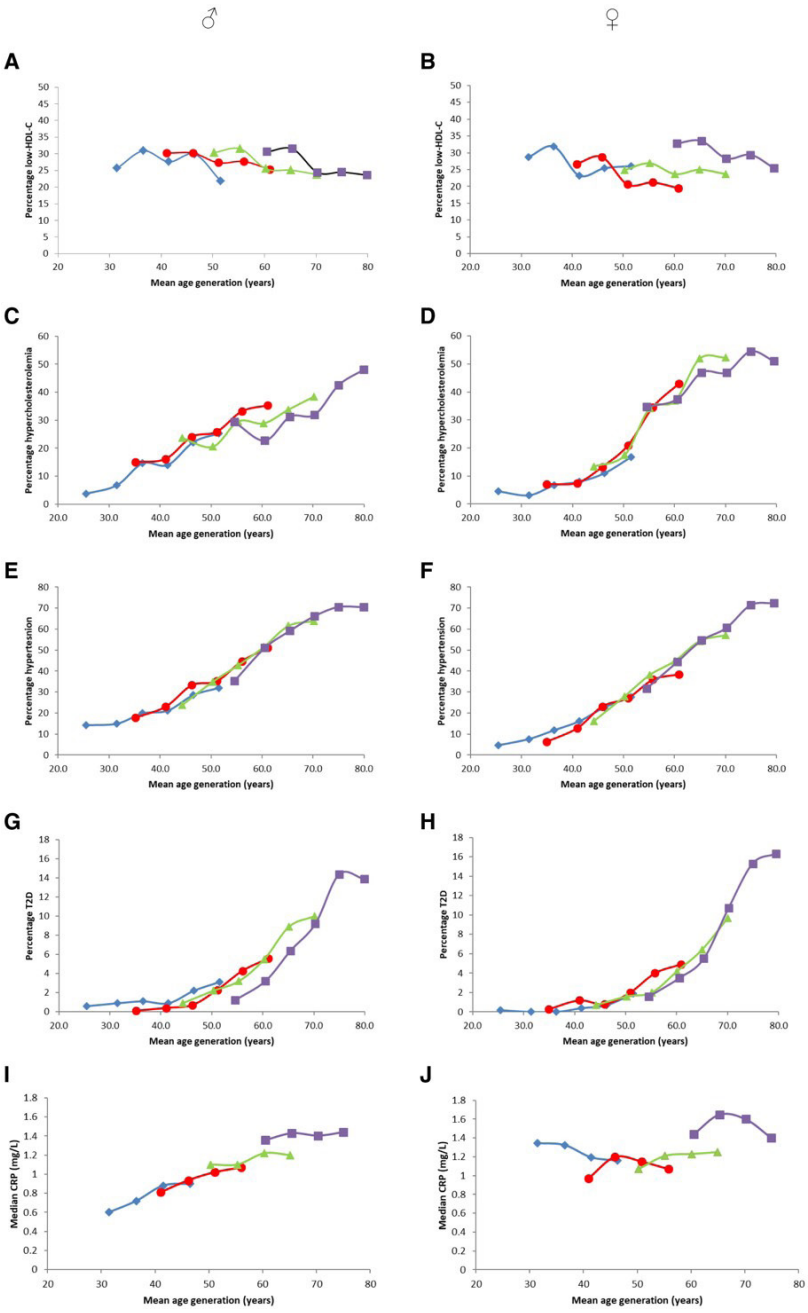

Figure 3. Age-specific prevalence of cardiometabolic risk factors over 26 years follow-up (6 rounds) in those who were in their 20s (20-29; -♦-(blue)), 30s (30-39; -●-(red)), 40s (40-49; -▲ -(green)), and 50s (50-59; - ■ -(purple)) at baseline, stratified by sex : low HDL-C (A,B), hypercholesterolemia (total cholesterol 6,5 mmol/l and/or on cholesterol lowering medication) (C,D), hypertension (E,F), type 2 diabetes (G,H), C-reactive protein (CRP) expressed as median (interquartile range) (I,J).

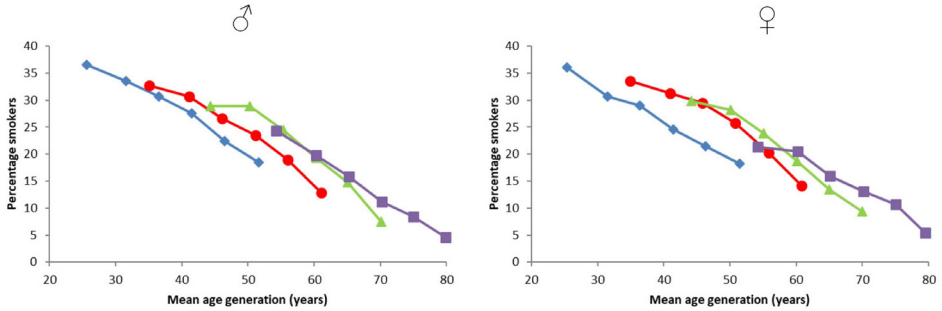

Figure 4. Age-specific prevalence of current smoking over 26 years follow-up (6 rounds) in those who were in their 20s (20-29; -♦-(blue)), 30s (30-39; -●-(red)), 40s (40-49; -▲-(green)), and 50s (50-59; - ■ -(purple)) at baseline, stratified by sex .

cohort (Figure 4). Prevalence of current smoking decreased with age in both sexes and all generations. Furthermore, for both men and women, a favorable generation shift was observed in the younger generations compared to the older ones ($p<0.05$).

DISCUSSION

Our results show that the prevalence of overweight and obesity increased with age and reached a sex-specific plateau at late midlife. This was apparent for all generations of men and women, except for the oldest generation of women, whose BMI still increased beyond late midlife. At the same age, the younger generations had higher weight, BMI, waist circumference, prevalence of overweight and obesity compared to the older generations but did not reach much higher levels in later life. In general, these developments did not translate into unfavourable generation shifts in cardiometabolic risk factors.

Evidence that younger birth generations are heavier than the ones born earlier was observed in high-income countries such as USA,[22,23] United Kingdom,[24] Australia,[11,25] Norway,[26] Finland[27] and Austria[28], as well as in middle-income countries such as China.[29] The Atherosclerosis Risk in Communities Study examined associations of age with mean BMI across three bi-ethnic birth cohorts (1920–1930, 1930–1935 and 1935–1945), 45 to 64 years of age and reported that except for white women, participants in the more recent cohorts gained more weight as they aged.[22] In our study, we observed unfavourable generation shifts in the anthropometric measures and obesity prevalence between every generation of men, whereas in women they were evident especially between the two youngest generations. Our results are in line with a recent Australian study [25] reporting a higher prevalence of obesity in women

born in 1989–1995 compared to women born in 1973–1978 when they were the same age. Other studies with similar age groups as in our cohort support the consistent unfavourable shifts we found among men, whereas their results for women partially contradict ours. For example, a Norwegian cohort study[26] with a comparable range of birth years to our DCS showed that BMI increased in every birth cohort of men and women during a 15-20-year period of follow-up. However, the study found that this increase was larger in the younger birth cohorts of men than the older ones, but did not differ among female birth cohorts. The lack of BMI differences in the female birth cohorts reported in these two studies contradicts the unfavourable BMI shift found between our two youngest generations of women. However, our study also showed that there was no difference in the BMI development up to 50 years among the other generations of women, which is in concordance with results from the two aforementioned studies.

The higher BMI and obesity prevalence observed in the oldest generation of women after the age of 50 years in our study could be due to several lifestyle and environmental factors. The number of children in the oldest generation was higher compared to the rest, which could be one factor explaining the differences in the obesity development of the oldest women. Previous research has demonstrated a positive association between parity (the number of times a woman has given birth) and obesity in women, particularly after menopause.[30] A study in middle-aged retired US women reported that women had a 7% increase in obesity for each additional child born, even after controlling for potential confounders.[31] From a biological point of view, this positive association of parity and obesity can be explained by the numerous metabolic changes that occur during the pregnancy and can persist even after, including insulin resistance and fat accumulation.[32,33]

Previously, we reported on 16 years of follow-up in the Doetinchem study [8] and already showed that the younger generations have overweight and obesity at a younger age. However, based on our follow-up of in total 26 years, we now observe that despite being having obesity at an earlier age, the younger generations do not reach much higher levels of BMI and obesity at midlife and beyond. This was an unanticipated observation, given the expected further rise of BMI throughout middle age. For example, when participants of the youngest generation were at an average age of 45, the obesity prevalence in men was 13.7% and after 5 years it reached 14.6%. This increase between the last two rounds was smaller than the increase in earlier rounds, which suggests that the rate of increase in obesity prevalence in the youngest generation of men starts to slow down after the age of 45 and points to a probable plateau in obesity after the age of 50. In women, the obesity prevalence

remained the same in the last two rounds, already showing evidence of a levelling off in obesity prevalence after the age of 50 in the younger generations. Therefore, data from the last 10 years of follow-up in the current study point to an obesity plateau in both men and women, which was somewhat unexpected. However, it is important to emphasize that even although the younger generations do not reach higher levels of obesity in later life, their lifetime exposure to obesity will be longer. This is of particular concern as an earlier exposure and longer duration of obesity have been shown to increase risk of several metabolic conditions, including T2D and CVD.[13-15]

It is important to mention that while BMI is the standard measure of overweight and obesity, it does not assess body composition or fat distribution. It has previously been shown that visceral fat, which is stored in the abdominal cavity, secretes more proinflammatory cytokines than other types of fat, which are thought to play an important role in the pathogenesis of insulin resistance and T2D.[34] Waist circumference is a simple way of assessing visceral fat and a higher waist circumference has also been associated with increased T2D risk.[35] In our study, the waist circumference followed a similar pattern to BMI, increasing more in the early development between each generation of men and the two youngest generations of women and starting to level off in the latest years of follow-up. These results point to increased weight-related chronic systemic inflammation in the younger generations, which could in turn increase the risk for T2D in these groups. However, in our study CRP levels, a marker for inflammation, were not higher in the younger generations compared to the older ones, but on the contrary in some generations of men and women CRP showed a favourable generation shift. In men, the lack of increased inflammation in the younger generations, given their unfavourable shifts in waist circumference, could be explained by the counterbalancing effects of decreased smoking prevalence in the recent generations of the Doetinchem study shown by Raho et al.[36] Our latest follow-up rounds further support this observation, pointing to favourable smoking generation shifts in men. Therefore, the reduced prevalence of smoking in the younger generations of men may have reversed the adverse effects of increased waist circumference and obesity on inflammation, which could in turn partially account for the general lack of unfavourable generation shifts in T2D prevalence. However, the unfavourable generation shift in T2D prevalence observed only between the two oldest generations of men suggests that in addition to reduced smoking prevalence, a possible delay between obesity and onset of T2D may explain the discrepant pattern of increased visceral fat and obesity without an increase in T2D prevalence. Among women, the large unfavourable generation shift in waist circumference and obesity that was found only between the two youngest

generations is probably not (yet) reflected in T2D shifts since the prevalence of diabetes is too low at that age. It is hard to predict the impact that increased obesity in the youngest generation of women will have on T2D prevalence in the future, if we take into consideration the large favourable shift in current smoking in the youngest generation of women, further supported by Raho et al.[36]

In our study, despite the increasing obesity prevalence in the younger generations, prevalence of hypertension and hypercholesterolemia showed in general no evident generation shifts in the younger individuals with more overweight and obesity. One explanation for these results could be the increased use in the last decades of antihypertensive and lipid-lowering medication, particularly among individuals with obesity.[37,38] In fact, in our data we observed that the younger generations used more antihypertensive and lipid-lowering medication compared to the older ones (data not shown).

Our study has some limitations that should be taken into account when interpreting the results. First, participants who take part in long-lasting prospective studies are usually slightly healthier and more educated than the general population. This means that the actual prevalence of obesity and cardiometabolic risk factors in the general Dutch population is probably slightly higher than presented in this study. However, the trends of anthropometrics and cardiometabolic risk factors in complete case analyses (including participants with measurements at all rounds) were similar to the trends in the main analyses (including participants with at least two measurements), indicating that they were not caused by a selective drop out during the follow-up (data not shown). Second, another limitation is that we did not examine specific trends in dietary intake and diet quality nor changes in physical activity. However, one of the strengths of the present study is the long follow-up period of 26 years, comprising six rounds of measurements. Another advantage is that we extensively studied multiple anthropometric traits including BMI, waist circumference, weight, prevalence of overweight and obesity.

In summary, we found that younger generations have a higher and earlier exposure to obesity but do not reach higher levels of BMI and obesity prevalence at midlife and beyond compared to the older generations. Although in general, these unfavourable generation shifts in anthropometric traits and prevalence of obesity were not associated with increased prevalence of cardiometabolic risk factors, the increased prevalence and duration of obesity in the younger generations should not be neglected, and might still lead to negative health effects further down the line. Since at the end of our follow-up the most recently born generations had reached

merely 50 years, further research beyond this age is needed to assess the progression of cardiometabolic and other obesity-related diseases in the current generations due to their long exposure to obesity. Furthermore, the observation that BMI plateaued for all younger generations at a similar level suggests that, apparently, at this plateau a population specific energy balance is reached. Research into the determinants of this state of energy balance could provide insight into population wide measures to decrease adiposity. This would require quantitative research to explore the effects of genetic influences, environmental factors and their interactions over the life course. Another consideration for future research would be on developing alternative markers that could better assess and capture adiposity and cardiometabolic health and disease such as metabolomics-based biomarkers. Finally, individuals with obesity in the current generations still have higher levels of cardiometabolic risk factors and risk of CVD than those with normal weight,[39,40] which calls for the need to maintain a healthy weight and prevent further increase in obesity in the current generations.

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