ARTICLE

Association of changes in body mass index during earlier adulthood and later adulthood with circulating obesity biomarker concentrations in middle-aged men and women

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Abstract

Aims/hypothesis The objective of our study was to investigate whether changes in BMI during earlier adulthood are more strongly associated with levels of circulating obesity biomarkers in middle age than are BMI changes during later adulthood.

Methods The study included 1,612 participants from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. The associations of BMI changes based on recalled BMI for the age ranges 25–40 years (earlier adulthood) and 40–55 years (later adulthood) with later biomarker levels were compared using a linear model, adjusted for BMI at age 25 years and conventional risk factors.

Results BMI changes during both time periods as well as BMI at age 25 years were significantly associated with circulating levels of adiponectin, γ-glutamyltransferase (GGT), alanine aminotransferase (ALT), high-sensitivity C-reactive protein (hs-CRP) and HDL-cholesterol (HDL-C) in both sexes, and of HbA_{1c} in women. However, BMI gain for the age range 25–40 years was significantly more strongly associated with unfavourable levels of adiponectin, hs-CRP, HDL-C and HbA_{1c} in men and women, and of GGT and ALT in men (p difference <0.05) than BMI gain for the age range 40–55 years. The percentage change in biomarker levels per unit gain in BMI for the age range 25–40 years ranged from 0.81% (HbA_{1c}) to 9.80% (hs-CRP) in men, and from 0.75% (HbA_{1c}) to 14.7% (hs-CRP) in women, whereas for the age range 40–55 years, values ranged from −0.15% to 4.82% in men and from 0.25% to 7.06% in women.

Conclusions/interpretation The results support the hypothesis that an increase in BMI in earlier adulthood is more strongly associated with unfavourable circulating levels of obesity biomarkers later in life than is an increase in BMI in later adulthood.

Abbreviations

ALT	Alanine aminotransferase
EPIC	European Prospective Investigation into Cancer and Nutrition
GGT	γ-Glutamyltransferase
HDL-C	HDL-cholesterol
hs-CRP	High-sensitivity C-reactive protein

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Introduction

Obesity is a well-established risk factor for cardiovascular disease, type 2 diabetes and other chronic diseases, but the

underlying mechanisms are not yet fully understood [1]. A number of biomarkers closely related to obesity have been proposed to be relevant for these associations, including markers of insulin sensitivity (e.g. adiponectin), glucose metabolism (e.g. HbA_{1c}), inflammation (e.g. C-reactive protein [CRP]), dyslipidaemia (e.g. HDL-cholesterol [HDL-C]) and hepatic fat accumulation (e.g. γ-glutamyltransferase [GGT] and alanine aminotransferase [ALT]). Lifestyle and surgical intervention studies have shown that weight loss is strongly associated with improved insulin sensitivity and glucose metabolism, as well as with decreased levels of liver enzymes [2–4]. However, recent studies suggest that disease risk may depend not only on the degree of adiposity, but also on body weight fluctuations during specific stages in life. For example, it has been shown that weight gain in earlier adulthood (i.e. between 25 and 40 years of age) is related to a higher risk and earlier onset of type 2 diabetes than weight gain in later adulthood (i.e. between 40 and 55 years of age) [5]. Yet surprisingly little is known about the extent to which BMI history or weight changes during life predict circulating levels of obesity biomarkers beyond the degree of adiposity.

In the present population-based study we aimed to investigate whether changes in BMI during earlier adulthood (age 25–40 years) are more strongly associated with levels of circulating obesity biomarkers (including adiponectin, GGT, ALT, HbA_{1c}, HDL-C and high-sensitivity CRP [hs-CRP]) in middle-aged men and women than changes in BMI in later adulthood (age 40–55 years).

Methods

The European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study is part of EPIC, a multi-centre prospective cohort study designed to investigate the association between nutrition, cancer and other chronic diseases [6, 7]. In Potsdam, Germany, a total of 27,548 individuals (16,644 women aged 35–65 years and 10,904 men aged 40–65 years) from the general population were recruited between 1994 and 1998 [8]. The health examination included anthropometric measurements, a personal health interview, a health questionnaire and blood sampling. The presence of diabetes mellitus at baseline was evaluated by a physician using information on self-reported medical diagnoses, medication records and dieting behaviour. Informed consent was obtained from all participants, and approval was given by the Ethical Committee of the State of Brandenburg, Germany.

The present study was based on a sub-cohort of 2,500 individuals who were selected at random from the total EPIC-Potsdam study population as part of separate case–cohort studies on biomarkers and risk of type 2 diabetes and cardiovascular diseases [9, 10]. For these study participants,

data on all biomarkers were available for 2,204 individuals, of whom 1,639 had data available on weight history (Fig. 1a). Finally, after further exclusion of individuals with implausible data on changes in BMI (i.e. an increase of >25 kg/m^2 or a decrease of >15 kg/m^2) during each weight-change period, a total of 1,612 men and women remained for analysis.

Body weight and height were measured during the health examination by trained members of staff following standardised procedures while the study participants were wearing only underwear and no shoes [11]. During the personal computer-based interview, the participants were asked to state their weight at ages 25 and 40 years [8]. A high degree of reproducibility of self-reported recalled body weight at ages 25 and 40 years between two interviews administered 1 year apart was observed in a sub-study of the EPIC-Potsdam Study. Reproducibility of weight recall as classification into recall error strata within 3 kg was 75.8% at age 25 years and 81.7% at age 40 years [12].

Red blood cell levels of HbA_{1c} were measured using HPLC according to the manufacturer's instructions (Tosoh,
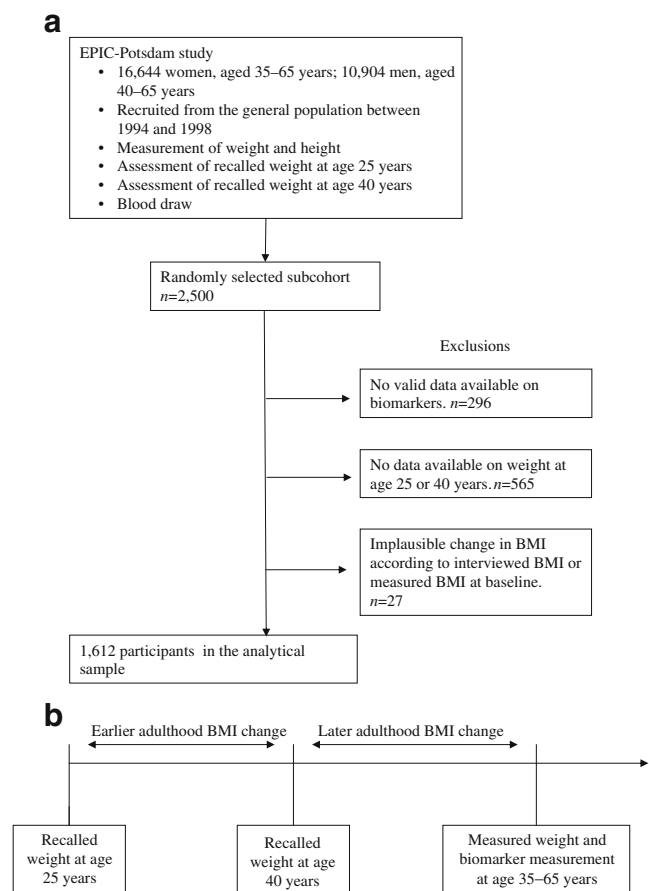
Fig. 1 a Reason for and number of excluded participants and (b) summary of weight history measurement

Stuttgart, Germany). Plasma levels of ALT, GGT, HDL-C and hs-CRP were determined using the automatic ADVIA 1650 analyser (Siemens Medical Solutions, Erlangen, Germany). The total adiponectin concentration was measured by ELISA (Linco Research, St Charles, MI, USA) [13]. All assay procedures were performed as described by the manufacturer.

We calculated the change in BMI between the ages of 25 and 40 years and between the age of 40 years and age at the time of recruitment (Fig. 1b). Because the time period between age 40 years and the time of recruitment varied across the study participants and was on average shorter (median 13 years) than the 15-year period between the ages of 25 and 40 years, we estimated the BMI change for a standardised 15-year period after age 40 years by linear regression [5]. The association between change in BMI and biomarker levels at the time of recruitment was investigated using general linear models. As a standard method in life-course epidemiology, BMI at recruitment was calculated as the sum of BMI at age 25 years, BMI change between the ages of 25 and 40 years, and BMI change between the age of 40 years and age at the time of recruitment [14]. Since the distributions of the levels of circulating biomarkers were right-skewed, log-transformed values were used in all analyses, and the strength of the associations was expressed as the percentage change in biomarker values by one unit change in the BMI component. In further analyses, categories of BMI change during each 15-year time period were formed as follows: (1) loss or stable (loss or gain of <1 kg/m^2 over 15 years); (2) moderate gain (gain of 1.0–4.0 kg/m^2); (3) severe gain (gain of >4.0 kg/m^2). We then cross-tabulated these categories and calculated the adjusted geometric means with 95% CI of biomarker levels. Analyses were adjusted for age, sex, BMI at age 25 years (continuous), education (in or no training, vocational training, technical school, or technical college or university degree), occupational activity (light, moderate or heavy), sports activity (0, 0.1–4 or >4 h/week), cycling (0, 0.1–2.4, 2.5–4.9 or ≥5 h/week), smoking (never, past, current ≤20 cigarettes/day or current >20 cigarettes/day) and alcohol intake (0, 0.1–5, 5.1–10, 10.1–20, 20.1–40 or >40 g/day). In sensitivity analyses we restricted the population to the 642 men and 885 women who had no history of diabetes at the time of recruitment (based on self-reported diagnosis, medication use or dietary treatment), and who were aged 50–65 years at the time of recruitment. All analyses were performed separately for men and women. We evaluated potential effect modifications by sex of the association between BMI change and circulating biomarker levels by modelling interaction terms for sex and BMI change categories. All statistical analyses were performed using SAS release 9.1 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided, and p values <0.05 were considered to be statistically significant.

Results

The mean BMI at age 25 years was 23.5 kg/m^2 in men and 22.2 kg/m^2 in women. The personal characteristics of the participants at the time of recruitment according to BMI categories at age 25 years are presented in Table 1. Men with BMI >30 kg/m^2 at age 25 years tended to report slightly higher levels of sports activity at recruitment than men with lower BMI levels (Table 1), whereas women with BMI >30 kg/m^2 at age 25 years tended to report less sports and biking activities than women with lower BMI levels. For both men and women, the percentage of individuals with a university degree and the mean alcohol consumption were lower among obese participants at age 25 years than in those with a lower BMI (Table 1). Of the biomarkers, higher plasma concentrations of GGT, hs-CRP and HbA$_{1c}$ were observed among obese men and women than among their counterparts with a lower BMI. Between the ages of 25 and 40 years the average BMI increased by 1.9 kg/m^2 in men and by 1.7 kg/m^2 in women, whereas between the ages of 40 and 55 years the average BMI increased by 2.0 kg/m^2 in men and by 3.2 kg/m^2 in women.

To investigate whether the association of BMI changes with biomarker levels differs between early and later adulthood, we included BMI at age 25 years and BMI changes between the ages of 25 and 40 years and between the ages of 40 and 55 years simultaneously in one model, and adjusted for age, sports activity, biking, education, occupational activity, smoking and alcohol consumption. We analysed men and women separately, as a significant interaction between sex and BMI change between the ages of 25 and 40 years was observed for ALT and hs-CRP, as well as between sex and BMI change between the ages of 40 and 55 years for hs-CRP and HbA$_{1c}$ (p interaction <0.05). We found that BMI at age 25 years as well as changes in BMI between 25 and 40 years of age and between 40 and 55 years of age were each significantly related to circulating levels of adiponectin, GGT, ALT, hs-CRP and HDL-C in men, and to circulating levels of adiponectin, GGT, ALT, hs-CRP, HDL-C and HbA$_{1c}$ in women (Table 2). In men, a change in BMI between 25 and 40 years of age was more strongly related to circulating biomarker levels than was a change in BMI between 40 and 55 years of age (p=0.04 for adiponectin, p=0.02 for GGT, p=0.003 for ALT, p=0.04 for hs-CRP, p=0.005 for HDL-C, and p<0.001 for HbA$_{1c}$). For example, adjusted for BMI at age 25 years, among men a one unit gain in BMI between ages 25 and 40 years was associated with 9.80% (95% CI 5.49–14.1) higher hs-CRP levels, whereas a one unit gain in BMI between ages 40 and

Table 1 Characteristics of analytical sample at the time of recruitment across the categories of BMI (kg/m^2) at age 25 years in men and women

Characteristic	Men (n=686)			Women (n=926)		
	<25 (n=533)	25–29.9 (n=135)	≥30 (n=18)	<25 (n=810)	25–29.9 (n=100)	≥30 (n=16)
Age (years)	53.0±7.46	54.6±7.22	54.7±7.12	52.5±6.96	55.2±7.56	55.4±5.67
BMI at age 25 years (kg/m^2)	22.6±1.54	26.4±1.15	33.0±3.09	21.6±1.84	26.6±1.31	33.0±2.39
BMI at age 40 years (kg/m^2)	24.7±2.45	28.1±2.24	32.0±4.66	23.4±2.75	28.0±3.04	32.6±4.77
BMI at age 55 years (kg/m^2)	26.5±4.84	30.4±4.93	35.4±10.4	26.6±5.37	31.8±6.86	34.8±7.74
Sports activity (h/week)	0.99±1.86	0.99±1.97	1.19±1.85	0.94±1.60	0.74±1.38	0.47±0.76
Biking (h/week)	1.71±2.52	2.06±3.20	1.69±2.49	1.86±3.05	1.64±2.97	1.38±2.00
Alcohol consumption (g/day)	23.0±21.7	20.3±19.2	13.3±10.4	8.14±9.55	7.94±10.9	5.75±5.80
Current or former smoker (%)	71.7	69.6	77.8	35.1	45.0	56.3
University degree (%)	54.6	44.4	33.3	28.3	13.0	18.8
Heavy physical work (%)	10.5	14.1	5.56	2.84	7.00	0.00
Prevalent diabetes (%)	4.50	11.1	27.8	3.09	14.0	12.5
Adiponectin (µg/ml)	5.64 (5.42–5.88)	5.08 (4.69–5.50)	5.58 (4.72–6.60)	8.62 (8.36–8.88)	7.80 (7.00–8.68)	6.33 (4.86–8.26)
GGT (U/l)	28.0 (26.1–30.1)	31.9 (28.1–36.3)	35.0 (21.9–55.9)	14.3 (13.6–15.1)	17.8 (15.2–20.5)	23.0 (15.2–34.9)
ALT (U/l)	25.5 (24.4–26.5)	29.6 (26.9–32.6)	24.8 (20.4–30.2)	16.9 (16.4–17.4)	20.2 (18.5–22.1)	21.4 (17.2–26.7)
hs-CRP (mg/l)	0.64 (0.23–0.24)	0.94 (0.24–0.25)	1.48 (0.24–0.27)	0.80 (0.24–0.24)	1.37 (0.23–0.25)	2.16 (0.15–0.29)
HDL-C (mmol/l)	1.18 (1.16–1.21)	1.11 (1.07–1.16)	1.00 (0.89–1.13)	1.42 (1.39–1.44)	1.27 (1.20–1.34)	1.36 (1.24–1.50)
HbA$_{1c}$ (%)	6.57 (6.50–6.64)	6.80 (6.65–6.96)	7.71 (6.98–8.52)	6.47 (6.42–6.52)	6.81 (6.60–7.03)	6.67 (6.14–7.25)

Values are means±SD, percentages for categorical variables and geometric means with 95% CI for biomarker variables

55 years was associated with 4.82% (95% CI 2.59–7.05) higher hs-CRP levels (p=0.04). In women, a change in BMI between the ages of 25 and 40 years was significantly more strongly associated with circulating levels of adiponectin (p=0.006), hs-CRP (p<0.001), HDL-C (p< 0.001) and HbA$_{1c}$ (p=0.004) than BMI gain between the ages of 40 and 55 years. In women, no significant difference between the age ranges in the strength of the association was observed for liver enzymes (p=0.17 for GGT, p=0.32 for ALT). Exclusion of individuals younger

Table 2 Adjusted percentage change (95% CI) in biomarker values per one unit increment of BMI at age 25 years, and per unit gain in BMI for the age ranges 25–40 and 40–55 years

Variable	BMI at age 25 years	BMI gain between 25 and 40 years of age	BMI gain between 40 and 55 years of age	p value[a]
Men				
Adiponectin	−2.71 (−4.08, −1.34)	−3.41 (−4.96, −1.85)	−1.62 (−2.43, −0.81)	0.04
GGT	4.27 (1.91, 6.62)	5.38 (2.71, 8.05)	1.67 (0.28, 3.05)	0.02
ALT	2.81 (1.36, 4.27)	4.59 (2.94, 6.24)	1.75 (0.90, 2.60)	0.003
hs-CRP	9.47 (5.68, 13.26)	9.80 (5.49, 14.10)	4.82 (2.59, 7.05)	0.04
HDL-C	−1.97 (−2.73, −1.21)	−1.91 (−2.77, −1.04)	−0.52 (−0.97, −0.08)	0.005
HbA$_{1c}$	1.28 (0.90, 1.67)	0.81 (0.38, 1.25)	−0.15 (−0.37, 0.08)	<0.001
Women				
Adiponectin	−1.66 (−2.72, −0.60)	−3.38 (−4.58, −2.18)	−1.42 (−2.05, −0.80)	0.006
GGT	2.99 (1.20, 4.78)	4.37 (2.35, 6.38)	2.73 (1.68, 3.79)	0.17
ALT	2.30 (1.29, 3.32)	2.52 (1.37, 3.66)	1.85 (1.25, 2.45)	0.32
hs-CRP	8.92 (5.92, 11.92)	14.7 (11.4, 18.1)	7.06 (5.29, 8.82)	<0.001
HDL-C	−1.28 (−1.87, −0.70)	−2.44 (−3.10, −1.79)	−0.68 (−1.02, −0.34)	<0.001
HbA$_{1c}$	0.45 (0.19, 0.71)	0.75 (0.46, 1.04)	0.25 (0.09, 0.40)	0.004

Adjusted by modelling. Multivariate model included age, sports activity, biking, education, occupational activity, smoking and alcohol consumption as well as BMI at age 25 years, BMI gain between ages 25 and 40 years, and BMI gain between ages 40 and 55 years

[a] Difference between age ranges 25–40 and 40–55 years

than 50 years or older than 64 years and those with diagnosed diabetes at the time of recruitment did not materially change the results (data not shown). However, in women, besides liver enzymes the difference between the age ranges 25–40 and 40–55 years did not remain significant for HbA_{1c} ($p=0.22$).

To shed light on the observed difference between time periods in the association of BMI change with biomarker values we cross-classified individuals on the basis of three categories of BMI change (loss or stable, moderate gain, and severe gain) in earlier adulthood and later adulthood. In general, higher geometric mean values of GGT, ALT, hs-CRP and HbA_{1c} and lower values for adiponectin and HDL-C were observed among individuals with severe BMI gain in both time periods compared with those with loss or stable or moderate weight gain in both time periods (Fig. 2a,b, and electronic supplementary material [ESM] Table 1). However, in both sexes, those with severe BMI gain in the age range 25–40 years but BMI loss or stable BMI in the age range 40–55 years tended to have higher values of GGT and HbA_{1c} and lower levels of adiponectin and HDL-C than individuals with weight loss or stable weight between the ages of 25 and 40 years but severe weight gain between the ages of 40 and 55 years. For example, among men whose BMI increased severely between ages 25 and 40 years but was stable or decreased between ages 40 and 55 years, the geometric mean HbA_{1c} level was 7.05% (95% CI 6.64%–7.14%), whereas in men with weight loss or stable weight between ages 25 and 40 years but severe weight gain between ages 40 and 55 years the geometric mean HbA_{1c} value was 6.69% (95%

CI 6.38%–7.01%) when adjusted for age, BMI at age 25 years, sports activity, biking, education, occupational activity, smoking and alcohol consumption. Exclusion of individuals with a BMI of 30 kg/m^2 or more at age 25 years did not materially alter the results (data not shown).

Discussion

In the present study, BMI at age 25 years as well as BMI change in earlier adulthood (age range 25–40 years) and later adulthood (age range 40–55 years) were each significantly associated with circulating plasma levels of adiponectin, GGT, ALT, hs-CRP and HDL-C in middle-aged men and women, and with HbA_{1c} in women. The association with circulating levels of obesity biomarkers in middle age was stronger for BMI change during earlier adulthood than for that during later adulthood for adiponectin, GGT, ALT, hs-CRP, HDL-C and HbA_{1c} in men, and for adiponectin, hs-CRP, HDL-C and HbA_{1c} in women. This suggests that BMI gain during earlier adulthood may be more important in determining these obesity biomarker levels than an increase in BMI later in life.

Obesity is a well-known risk factor for the development of insulin resistance, steatohepatosis and dyslipidaemia. The adipose tissue is capable of producing pro-inflammatory cytokines and hormones, which may systemically affect lipoprotein metabolism and insulin sensitivity [15]. In the present study, we examined biomarkers related to obesity that may be relevant for the development of
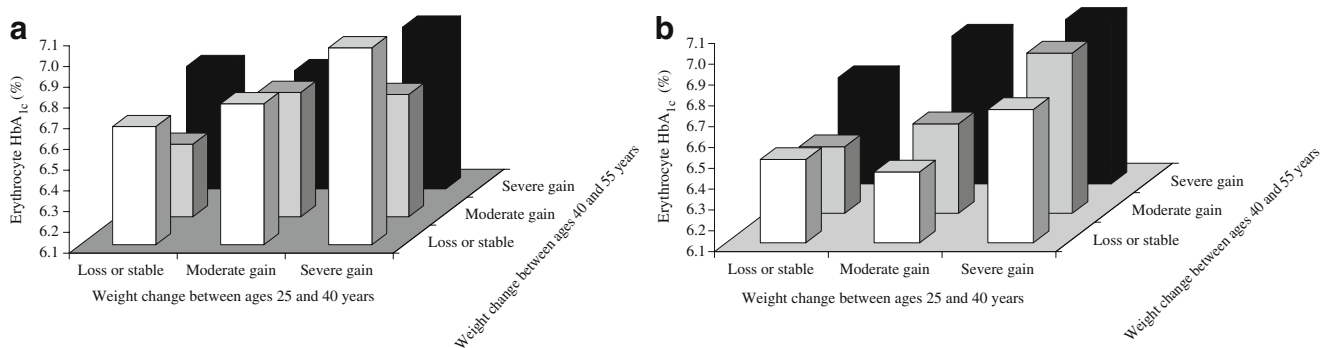
Fig. 2 Adjusted geometric mean values (adjusted for age, sports activity, biking, education, occupational activity, smoking and alcohol consumption and BMI at age 25 years) of HbA_{1c} (%) according to categories of BMI changes between ages 25 and 40 years (on x-axis) and changes between ages 40 and 55 years (on y-axis) in (**a**) men and (**b**) women. In men, the geometric mean values across the increasing categories of weight gain between ages 40 and 55 years among those with a decrease in or stable BMI between ages 25 and 40 years were 6.67 (95% CI 6.46–6.88), 6.45 (95% CI 6.23–6.68) and 6.69 (95% CI 6.38–7.01); among men with a moderate increase in BMI between ages 25 and 40 years the geometric mean HbA_{1c} values were 6.78 (95% CI 6.57–6.99), 6.70 (95% CI 6.50–6.92) and 6.67 (95% CI 6.43–6.92); and among men with severe BMI gain between ages 25

and 40 years they were 7.05 (95% CI 6.74–7.37), 6.69 (95% CI 6.28–7.13) and 6.88 (95% CI 6.49–7.29). In women, the geometric mean values across the increasing categories of weight gain between ages 40 and 55 years among those with a decrease in or stable BMI between ages 25 and 40 years were 6.50 (95% CI 6.33–6.69), 6.42 (95% CI 6.25–6.60) and 6.61 (95% CI 6.41–6.82); among women with moderate BMI gain between ages 25 and 40 years the corresponding geometric mean HbA_{1c} values were 6.44 (95% CI 6.26–6.64), 6.53 (95% CI 6.36–6.71) and 6.81 (95% CI 6.63–7.01); and among women with severe BMI gain between ages 25 and 40 years HbA_{1c} values across the increasing categories of BMI change between ages 40 and 55 years were 6.74 (95% CI 6.48–7.01), 6.87 (95% CI 6.60–7.16) and 6.89 (95% CI 6.64–7.14)

chronic diseases, including markers of insulin sensitivity, glucose metabolism, inflammation, dyslipidaemia and hepatic fat accumulation. Several studies have suggested an association between an increase in BMI in adulthood and unfavourable lipid profiles [16–19] and onset of type 2 diabetes [20–30] as well as cardiovascular diseases after adjustment for attained weight at entry to the study [31–37]. However, although the association between obesity and risk of various chronic diseases is well documented, there is only limited information about the question of whether the time of onset of obesity or changes in BMI throughout life affects metabolism or disease risk beyond adiposity. The results of the present study suggest that an increase in BMI in earlier adulthood (age 25–40 years) may be more important for determining the metabolic profile related to disease risk at about 60 years of age than BMI gain in later adulthood. These results are consistent with the few previous studies that have simultaneously compared the associations between different weight history components and disease risk, including the risk of type 2 diabetes [5] and of metabolic syndrome [38]. Thus in the EPIC-Potsdam study it was previously shown that severe BMI gain in earlier adulthood was associated with a considerably higher (1.5 times higher in men and 4.3 times higher in women) diabetes risk compared with BMI gain in later life [5]. In the US National Health and Nutrition Examination Survey, weight gain between the ages of 25 and 40–54 years suggested stronger associations with the presence of the metabolic syndrome as well as with lower plasma HDL-C and higher triacylglycerol values than did weight gain between the ages of 40–54 and 60 years [38]. Overall, these observations suggest that susceptibility to the development of diseases and abnormal metabolic profiles related to obesity may be time dependent, although the underlying mechanisms for such time dependency are unknown. Alternatively, one may speculate whether individuals who showed an increase in BMI in later adulthood may differ from those who gained weight in earlier adulthood in behavioural or genetic characteristics that may affect metabolism and risk profiles. For example, an increase in BMI in later adulthood may be more likely to be a result of a sedentary lifestyle, whereas BMI gain in earlier life may be more strongly related to genetic factors, and these factors may differ in their impact on metabolism and disease risk. In addition, the possibility cannot be ruled out that the longer duration of obesity among individuals whose BMI increased between the ages of 25 and 40 years is a significant factor contributing to metabolic disturbances reflected by biomarkers in the present study. Among women, one further explanation for the stronger association of the BMI increase during earlier adulthood with unfavourable circulating biomarker levels may be the childbearing years, which have been shown to be associated with the development of obesity [39–41]. However, a similarly stronger association of the BMI increase during earlier adulthood with unfavourable circulating biomarker levels was observed in men. Clearly, further studies are warranted to shed more light on the potential time dependency of the effects of obesity on metabolism, biomarkers and disease risk.

Some limitations of this study need to be considered. One limitation was that information on body weight at ages 25 and 40 years was self-reported, whereas weight and height at baseline were measured by trained staff. Although acceptable agreement between self-reported retrospective body weight and measured body weight has been shown [42, 43], it is possible that misclassification due to under-reporting of past weight by overweight participants and over-reporting by underweight participants may have occurred, which could influence the results. In the present study, we only had data available from a single blood sampling, which might have introduced random measurement errors in determining biomarkers. However, most of the markers presented here have been shown to have a suitable reliability for epidemiological studies [44, 45]. Circulating HbA$_{1c}$ values tended to be slightly higher than expected. This may be due to the storage conditions for our blood samples. However, since the validity of the results on the association between exposure and outcome in epidemiological studies depends primarily on the ranking of individuals based on a biomarker rather than the absolute values, given that the ranking remains the same, the slightly overestimated HbA$_{1c}$ levels do not affect the validity of our conclusions.

In summary, the present study demonstrated that among middle-aged men and women, an increase in BMI during earlier adulthood is more strongly associated with unfavourable circulating levels of obesity biomarkers than an increase in BMI during later adulthood. This suggests that metabolic susceptibility to changes in BMI varies according to age. The result is in line with studies which suggest that an increase in BMI in earlier adulthood is a stronger risk factor for diabetes or the metabolic syndrome than weight gain in later life [5, 38]. These results also support the hypothesis that a comprehensive history of weight gain in earlier adult life may provide a more precise risk assessment than a single measurement of BMI in later adulthood. Finally, the results of the present study highlight the importance of preventing weight gain in earlier adulthood.

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