Childhood underweight, weight gain during childhood to adolescence/young adulthood and incidence of adult metabolic syndrome in the SUN (Seguimiento Universidad de Navarra) Project

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Abstract

Objective: To assess associations between childhood body weight, weight gain during childhood to adolescence/young adulthood and incidence of adult metabolic syndrome (MetS).
Design: A dynamic prospective cohort study (the SUN Project; Seguimiento Universidad de Navarra). Participants were asked to select which of nine body images most closely represented their body shape at ages 5 and 20 years, and it was used as a proxy of BMI. An incident case of MetS was diagnosed according to criteria of the International Diabetes Federation. Associations between childhood body weight, weight gain during childhood to adolescence/young adulthood and incidence of adult MetS were estimated by multiple-adjusted odds ratios and their 95% confidence intervals.
Setting: University of Navarra, Spain.
Subjects: The study included 5317 university graduates, followed-up for a median of 6·1 years.
Results: The incidence of MetS was 2·9% (1·7% in women and 5·1% in men). Among men, body shape at age 5 years was inversely related to adult MetS (OR = 0·83, 95% CI 0·72, 0·97), whereas weight gain during childhood to adolescence/young adulthood was directly associated with adult MetS (OR = 1·49, 95% CI 1·01, 2·18); both childhood underweight (OR = 5·20, 95% CI 1·87, 14·50) and childhood obesity (OR = 4·66, 95% CI 1·40, 15·51) increased the likelihood of adult MetS. No association was apparent among women.
Conclusions: These results support treating childhood underweight and weight gain during childhood to adolescence/young adulthood as part of comprehensive adult MetS prevention efforts in men.

Metabolic syndrome (MetS) is characterized by the clustering of cardiovascular risk factors such as obesity, dyslipidaemia, insulin resistance, hyperinsulinaemia, glucose intolerance and hypertension[1]. This syndrome is recognized as an important public health concern worldwide, owing to its prevalence of over 20% in adult populations around the world[1–4] and also to its strong association with CVD and type 2 diabetes, both main causes of death on a global scale[1,5,6].

In general, there are differences in the prevalence of MetS and its components among men and women. MetS has been more frequent in men than in women, but the prevalence has risen particularly in young women, where it is mainly driven by obesity. Furthermore, the presence of impaired glucose tolerance is higher among women, whereas the other MetS components are more common among men until women enter the menopause period[7].

Some studies have also consistently shown high rates of MetS in people who were born small, because insulin resistance, which is recognized as a key element of this syndrome[8], could be a genetically 'programmed' response to fetal undernutrition[9]. However, this hypothesis has been criticized for the reason that the prevalence of underweight newborn children is decreasing whereas the

frequency of MetS is increasing in Western countries. Thus, it has been suggested that the origin of adulthood risk of this syndrome and other chronic diseases could be associated with somatic growth during childhood, and not necessarily to intra-uterine growth[10]. The weight change at different periods of early life may have differential effects on the acquisition of fat or lean adult mass and on the development of chronic disorders[11].

Therefore, the aim of the present study was to assess the associations between childhood body weight, weight gain during childhood to adolescence/young adulthood and incidence of adult MetS among participants in the SUN (Seguimiento Universidad de Navarra, University of Navarra Follow-up) Project, a dynamic cohort study.

Methods

Study population

The SUN Project is a multi-purpose, dynamic Spanish cohort based on former students of the University of Navarra, registered professionals from some Spanish provinces and university graduates from other associations[12]. Information on exposure and outcome is gathered by mailed questionnaires collected biennially. Persons who do not reply to the follow-up questionnaires are sent up to five additional mailings.

The baseline questionnaire included 554 questions about a wide array of characteristics: sociodemographic (e.g. sex, age, marital status), anthropometric (e.g. weight, height), body shape at ages 5, 20, 30 and 40 years (e.g. nine-level body image scheme in each age), lifestyle and health-related habits (e.g. smoking status, physical activity), diet (e.g. food consumption, alcohol intake), obstetric history for women (e.g. pregnancy) and medical history (e.g. prevalence of diseases – including hypertension, diabetes, obesity, dyslipidaemia, cancer, myocardial infarction, stroke and atrial fibrillation – and medication use). The 2-year, 4-year, 6-year and 8-year follow-up questionnaires queried changes in some characteristics presented above (weight, lifestyle and health-related habits, diet, incidence of disease, pregnancy). The last two questionnaires also gathered additional information like self-reported waist circumference (cm), blood pressure (mmHg), TAG (mg/dl), HDL cholesterol (HDL-C; mg/dl) and plasma glucose (mg/dl).

The recruitment of participants started in December 1999 and is permanently ongoing because it is a dynamic cohort. The overall follow-up rate approaches 90 %. Before June 2006, 15 786 participants had answered the baseline questionnaire. From them, we excluded participants lost to follow-up (n 1449). Because the criteria to diagnose an incident case of MetS were collected only in the 6-year and 8-year follow-up questionnaires, persons who did not respond to these questionnaires were excluded, even though they answered other follow-up questionnaires (n 3621). Additionally, we also excluded participants with missing values for body weight variables (n 406); those who had chronic diseases (hypertension, diabetes, obesity and dyslipidaemia) at baseline, 2-year and 4-year follow-up (n 4697); those who reported extremely low (<3347 kJ/d for men, <2092 kJ/d for women) or high (>16 736 kJ/d for men, >14 644 kJ/d for women) values for total energy intake, because they were more likely to have failed to properly complete the questionnaire (n 254); and pregnant women (n 42). Some participants met more than one of these exclusion criteria. Finally, 5317 participants were included in analyses (median follow-up = 6·1 years).

The study was approved by the Institutional Review Board of the University of Navarra. Voluntary completion of the first questionnaire was considered to imply informed consent.

Childhood body weight, weight change during childhood to adolescence/young adulthood and baseline body weight assessment

Body shape was ascertained at the baseline questionnaire with a nine-level body image scheme (Fig. 1) which was validated by Stunkard and colleagues: body images F1/M1 to F3/M3 correspond to underweight (BMI <19·99 kg/m^2); body images F4/M4 and F5/M5 correspond to normal weight (BMI = 20·00–24·99 kg/m^2); body images F6/M6 and F7/M7 correspond to overweight (BMI = 25·00–29·99 kg/m^2); and body images F8/M8 and F9/M9 correspond to obesity (BMI ≥ 30·00 kg/m^2)[13].

Participants were asked to select which of the nine body images most closely represented their body shape at ages 5 and 20 years. The validity of the remote recall of body shape was assessed among 181 participants from the Third Harvard Growth Study. Pearson correlations between recalled body shape and BMI were 0·60 for age 5 years and 0·66 for age 20 years[14].

The weight gain during childhood to adolescence/young adulthood was estimated by the difference between body shapes at ages 5 and 20 years.

Participants' self-reported weight and height at the baseline questionnaire in the SUN Project were used to calculate BMI. This information was validated in a specific study; although correlation does not necessarily mean good agreement, BMI calculated with self-reported weight and height exhibited a high correlation with BMI calculated from measured weight and height (mean relative error = 1·4 %)[15].

Metabolic syndrome assessment

MetS was defined according to the International Diabetes Federation (IDF) criteria[16]. In the 6-year and 8-year follow-up questionnaires, self-reported information about these criteria was collected (waist circumference (cm), blood pressure (mmHg), TAG (mg/dl), HDL-C (mg/dl) and plasma glucose (mg/dl)). Waist circumference was
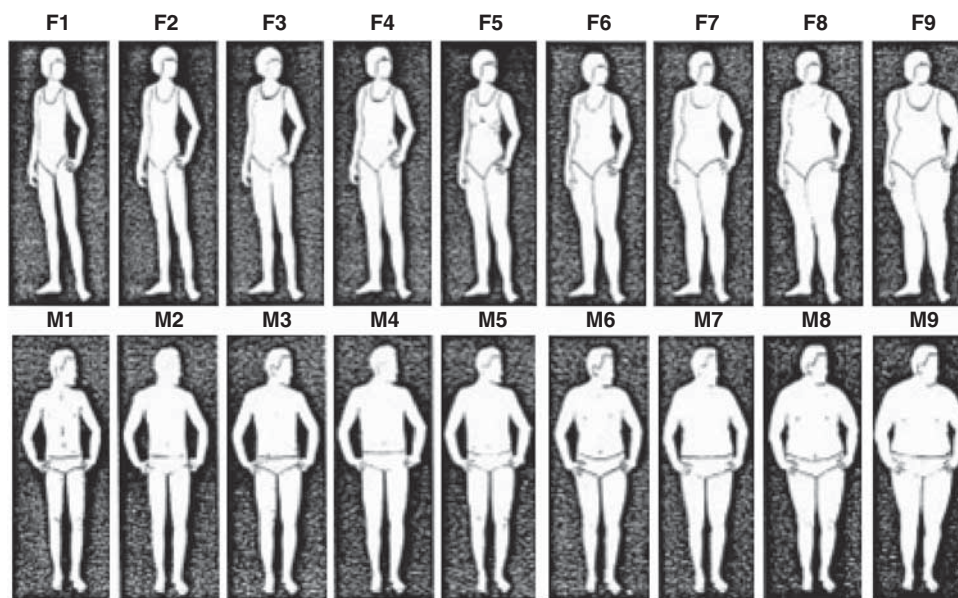
Fig. 1 Options presented to select body shape at age 5 and 20 years, according to sex. F = female; M = male; F1/M1 to F3/M3, underweight (BMI < 19·99 kg/m²); F4/M4 and F5/M5, normal weight (BMI = 20·00–24·99 kg/m²); F6/M6 to F9/M9, overweight or obese (BMI ≥ 25·00 kg/m²)

measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest[17]. All participants were sent a tape measure with the 6-year and 8-year follow-up questionnaires, and an explanation of how to measure their waist. If BMI was ≥30·00 kg/m², central obesity was assumed and waist circumference not taken into account[16].

The validities of the self-reported MetS components were assessed in a specific study with 287 participants in the SUN Project. Significant Pearson correlation coefficients (P < 0·001), range 0·5 to 0·9, between self-reported MetS components and their direct assessments by an experienced physician were demonstrated[18].

Statistical methods

The differences between the participants with respect to some characteristics were estimated with ANOVA or Pearson's χ^2 test.

Three non-conditional logistic regression models were fit. Two of them were fitted to assess the relationship between childhood body weight and incidence of adult MetS: (i) in the first model, OR and their 95 % CI were calculated considering the normal category of BMI at age 5 years (body images F4/M4 and F5/M5, corresponding to BMI = 20·00–24·99 kg/m²) as the reference; (ii) in the second model, OR and their 95 % CI were calculated considering the body shape at age 5 years as a continuous variable. The third model was fitted to assess the relationship between weight gain during adolescence/young adulthood and incidence of adult MetS: (iii) in this model, OR and their 95 % CI were calculated considering the weight gain from 5 to 20 years as a continuous variable. To avoid reverse causality, participants with age less than

or equal to 30 years at baseline (n 3273) were excluded from these analyses. Potential confounders included in all models were age and BMI at baseline.

All analyses were stratified by sex. All P values presented are two-tailed; P < 0·05 was considered statistically significant. The SPSS statistical software package for Windows version 15·0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

The median follow-up of the participants was 6·1 years. One hundred and fifty-five participants initially free of MetS were diagnosed as incident cases of this syndrome (sixty women and ninety-five men). The overall cumulative incidence of MetS in this population was 2·9 % during the follow-up period (1·7 % in women and 5·1 % in men, P < 0·001).

The characteristics of the participants according to MetS status and sex are shown in Table 1. In both sexes, participants with MetS were older and had higher BMI at baseline. Among participants with MetS, the incidence of each MetS component was as follows: abdominal obesity, 100·0 % in women and 100·0 % in men (this is a *sine qua non* according to the IDF definition); high blood pressure, 73·3 % in women and 72·6 % in men; hyperglycaemia, 61·7 % in women and 63·2 % in men; hypertriacylglycerolaemia, 45·0 % in women and 46·5 % in men; and low HDL-C, 38·3 % in women and 33·7 % in men. With respect to MetS components incidence according to sex in the whole population, abdominal obesity, hypertriacylglycerolaemia, hyperglycaemia and hypertension

Table 1 Characteristics of the study participants according to MetS status, stratified by sex: the SUN (Seguimiento Universidad de Navarra, University of Navarra Follow-up) Project

	MetS						
	Yes		No		Total		
	Mean or n	SD or %	Mean or n	SD or %	Mean or n	SD or %	P
FEMALE (n 3451)							
Age (years) (mean, SD)	44·6	10·7	33·0	9·0	33·2	9·2	<0·001†
BMI (kg/m^2) (mean, SD)*	24·0	2·4	21·4	2·4	21·4	2·3	<0·001†
MetS components (n, %)							
Abdominal obesity*	60	100·0	1329	39·2	1389	40·2	<0·001‡
Hypertriacylglycerolaemia*	27	45·0	53	1·6	80	2·3	<0·001‡
Low HDL-C	23	38·3	154	4·5	177	5·1	<0·001‡
Hyperglycaemia*	37	61·7	143	4·2	180	5·2	<0·001‡
Hypertension*	44	73·3	281	8·3	325	9·4	<0·001‡
MALE (n 1866)							
Age (years) (mean, SD)	45·6	12·0	37·3	10·7	37·7	10·9	<0·001†
BMI (kg/m^2) (mean, SD)*	25·7	2·0	24·2	2·2	24·3	2·2	<0·001†
MetS components (n, %)							
Abdominal obesity*	95	100·0	793	44·8	888	47·6	<0·001‡
Hypertriacylglycerolaemia*	44	46·3	57	3·2	101	5·4	<0·001‡
Low HDL-C	32	33·7	67	3·8	99	5·3	<0·001‡
Hyperglycaemia*	60	63·2	146	8·2	206	24·0	<0·001‡
Hypertension*	69	72·6	379	21·4	448	24·0	<0·001‡

MetS, metabolic syndrome; HDL-C, HDL cholesterol.
MetS components: abdominal obesity, waist circumference ≥80 cm in women or ≥90 cm in men or BMI ≥30 kg/m^2; hypertriacylglycerolaemia, TAG ≥150 mg/dl; low HDL-C, HDL-C <50 mg/dl in women or <40 mg/dl in men; hyperglycaemia, glucose ≥100 mg/dl; hypertension, blood pressure ≥130/85 mmHg.
*$P < 0·001$ (Pearson's χ^2 test) for comparison of incidence of MetS components between sexes.
†P from ANOVA.
‡P from Pearson's χ^2 test.

were more frequent among men than among women ($P < 0·001$). These associations remained statistically significant after adjusting for age (data not shown).

The main characteristics of the participants according to category of body shape at age 5 years and sex are presented in Table 2. In both sexes, participants who classified themselves as being in the lowest body shape category (F1/M1) were older and had a higher incidence of MetS. On the other hand, participants who classified themselves as being in the highest body shape category (F6/M6 to F9/M9) were mostly men. In both sexes, the participants in this group also had higher average BMI at baseline.

The association between childhood body weight (categorical variable) and the incidence of adult MetS, stratified by sex, is shown in Table 3. Among men, both childhood underweight (OR = 5·20, 95% CI 1·87, 14·50) and childhood obesity (OR = 4·66, 95% CI 1·40, 15·51) were associated with adult MetS after adjusting for age and BMI at baseline. No association was apparent among women.

The associations between childhood body weight (continuous variable), weight gain during adolescence/young adulthood (continuous variable) and incidence of adult MetS, stratified by sex, are presented in Table 4. Among men, body shape at age 5 years was inversely related to adult MetS after adjusting for age and BMI at baseline (OR = 0·83, 95% CI 0·72, 0·97). This estimate can be interpreted as follows: for each 1-unit increase in body shape at age 5 years, the likelihood of adult MetS decreased by 17%. On the other hand, weight gain

from 5 to 20 years of age was directly associated with adult MetS after adjusting for age and BMI at baseline (OR = 1·49, 95% CI 1·01, 2·18; Table 4), meaning that for each 1-unit increase in body shape from 5 years to 20 years, the likelihood of adult MetS increased by 49%. No association was apparent among women.

Discussion

Only among men, but not among women, we found that both childhood underweight and childhood obesity were associated with an increased risk of adult MetS; body shape at age 5 years was inversely and monotonically related to adult MetS. However, this association was reversed when we assessed change in body shape from 5 to 20 years. Weight gain during this period (childhood to adolescence/young adulthood) was associated with a higher risk of adult MetS.

Our findings are partially consistent with the results of a similar cohort study developed with 91 453 adult French women who were asked to report their body silhouette at various ages, although the outcome was not MetS but diabetes[19]. Nevertheless, MetS can be considered a pre-stage of diabetes[1]. In that French study, body silhouettes at 8 years, at menarche and in young adulthood (20 to 25 years) were inversely associated with the risk of diabetes, independently of adult BMI during follow-up. In mid-adulthood (35 to 40 years) the association was reversed,

Table 2 Characteristics of the participants according to childhood body shape, stratified by sex: the SUN (Seguimiento Universidad de Navarra, University of Navarra Follow-up) Project

	Childhood body shape												
	F1/M1		F2/M2		F3/M3		F4/M4		F5/M5		F6/M6 to F9/M9*		P
	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	
FEMALE (n, %)†	613	54·0	972	67·3	756	69·4	632	74·9	369	70·7	109	38·8	
Baseline age (years) (mean, SD)	36·9	10·7	33·3	9·1	31·9	8·3	31·8	8·6	32·5	8·6	31·8	7·3	<0·001‡
Baseline BMI (kg/m²) (mean, SD)	21·3	2·3	21·1	2·2	21·5	2·3	21·7	2·3	21·9	2·1	22·3	2·3	<0·001‡
MetS incidence (n, %)	20	3·3	18	1·9	5	0·7	6	0·9	10	2·7	1	0·9	0·003§
MALE (n, %)†	522	46·0	473	32·7	334	30·6	212	25·1	153	29·3	172	61·2	
Baseline age (years) (mean, SD)	41·7	11·4	37·7	10·7	35·8	10·7	35·4	9·4	34·7	9·7	34·8	9·9	<0·001‡
Baseline BMI (kg/m²) (mean, SD)	24·4	2·2	24·0	2·1	24·3	2·1	24·4	2·5	24·1	2·3	25·0	2·2	<0·001‡
MetS incidence (n, %)	42	8·0	23	4·9	17	5·1	3	1·4	1	0·7	9	5·2	0·001§

MetS, metabolic syndrome.
*This category includes the shapes F6/M6 up to F9/M9 because small sample sizes.
†$P < 0.001$ (Pearson's χ^2 test) for comparison of childhood body shape between sexes.
‡P from ANOVA.
§P from Pearson's χ^2 test.

with an increase in risk related to a large body silhouette. Furthermore, an increase in body silhouette from childhood to mild-adulthood amplified the risk of diabetes[19].

Three articles based on a cohort of 1492 men and women aged 26 to 32 years in Delhi (India) investigated the associations between patterns of infant, childhood and adolescent BMI and the incidence of chronic diseases in adulthood. Unlike our work and that done in France, BMI was calculated with directly measured weight and height. Despite the methodological dissimilarity, their results were in accordance with our findings. In one of these Indian studies, both lower BMI in infancy and rapid childhood BMI gain (2 to 11 years) were associated with an increased risk of adult MetS[20]. The results of the second study showed that the growth of children in whom impaired glucose tolerance or diabetes subsequently developed was characterized by low BMI between birth and 2 years of age, a young age at adiposity rebound (as defined by the age after infancy at which BMI starts to rise) and a sustained accelerated gain in BMI until adulthood[21]. The last Indian investigation presented important results for understanding which are the critical periods of early life when weight gain is likely to have differential effects on the acquisition of fat or lean adult mass and on the development of chronic disorders[11]. Lower BMI at age 2 years was associated with earlier adiposity rebound, and this last condition predicted an increase in all measurements of adult body composition except height. Furthermore, BMI gains during infancy and early childhood were more strongly correlated with adult lean residual mass than with adult adiposity or with central adiposity. Greater BMI gains in late childhood (approximately between the ages of 6 and 7 years) and adolescence were strongly associated with adult adiposity and central adiposity. Other works have shown that this last relationship increased the risk of adult hypertension[22], type 2 diabetes[23] and IHD[24].

A likely mechanism to explain the associations between low BMI in infancy, accelerated BMI gain in later childhood and adolescence, and adult chronic diseases includes a low adult muscle mass as a key element. Skeletal muscle cells lose their ability to divide in early postnatal life. Therefore, as has been demonstrated in animal models, undernutrition at this period of life permanently diminishes muscle mass whereas improved nutrition at later ages produces an excessive fat deposition[25]. Sachdev et al. proposed that infancy, like fetal life, is a critical phase for lean mass growth. So, the susceptibility of some persons to chronic diseases may partly be caused by poor development of lean mass in fetal life and infancy, combined with increased adiposity in later childhood[11].

With respect to MetS aetiology, excess body fat, especially visceral fat, mobilizes NEFA in the circulation. Afterwards, the rise of NEFA and their metabolites in insulin-sensitive tissues and cells, such as the hepatic and the muscular, promotes degradation in glucose capture

Table 3 Association between childhood body weight and incidence of adult MetS, stratified by sex: the SUN (Seguimiento Universidad de Navarra, University of Navarra Follow-up) Project

	Childhood body weight		
	Underweight (F1/M1 to F3/M3)	Normal weight (F4/M4 and F5/M5)	Overweight/obesity (F6/M6 to F9/M9)
FEMALE			
Cases	43	16	1
Total	2341	1001	109
MetS incidence/100	1·8	1·6	0·9
95 % CI	1·3, 2·5	0·9, 2·6	0·0, 5·0
Model			
OR	0·95	1·00	0·57
95 % CI	0·52, 1·75	Ref.	0·73, 4·42
MALE			
Cases	82	4	9
Total	1329	365	172
MetS incidence/100	6·2	1·1	5·2
95 % CI	5·0, 7·6	0·4, 3·0	2·4, 9·7
Model			
OR	5·20	1·00	4·66
95 % CI	1·87, 14·50	Ref.	1·40, 15·51

MetS, metabolic syndrome; Ref., reference category.
Model: OR and 95 % CI are adjusted for age and BMI at baseline.

Table 4 Association between childhood body weight, weight gain during childhood to adolescence/young adulthood and incidence of adult metabolic syndrome, stratified by sex: the SUN (Seguimiento Universidad de Navarra, University of Navarra Follow-up) Project

	OR	95 % CI	P
FEMALE			
Childhood body weight (continuous)	0·94	0·77, 1·14	0·508
Weight gain (continuous)	0·97	0·50, 1·87	0·921
MALE			
Childhood body weight (continuous)	0·83	0·72, 0·97	0·019
Weight gain (continuous)	1·49	1·01, 2·18	0·043

OR and 95 % CI are adjusted for age and BMI at baseline.

and insulin resistance. Moreover, the NEFA overflow to the liver stimulating glyconeogenesis, TAG production, VLDL cholesterol secretion and decreases insulin hepatic clearance[1,8].

In the presence of hypertriacylglycerolaemia, a diminution of the cholesterol content and an addition of TAG occur in HDL-C, making this lipoprotein small and dense. These alterations cause an increased HDL-C renal clearance, diminishing its levels in plasma[1,8].

As a product of the increased plasma glucose levels, there is a higher insulin release by the pancreas. This hyperinsulinaemia is associated with hypertension in the MetS aetiology because the insulin surplus leads to elevated renal sodium re-absorption, inducing a plasmatic volume expansion and, consequently, increasing the blood pressure. Furthermore, sympathetic nervous system activity is augmented in the hyperinsulinaemic state, promoting a higher adrenaline release. This neuro-hormone also increases the sodium re-absorption, the peripheral vasoconstriction, the heart rate, the adipose tissue lipolysis and the hepatic glyconeogenesis[1,8].

It could be contradictory to think of childhood underweight as a public health problem in Spain, given that childhood obesity has high rates in Western developed countries. However, a study that investigated the trends in excess weight and thinness among Spanish schoolchildren in the period 1992–2004 demonstrated that both problems have increased concurrently. The overall prevalence of overweight/obesity increased from 24·4 % in 1992 to 30·9 % in 2004 (P = 0·07), and the overall prevalence of thinness was 2·7 % in 1992 and 9·2 % in 2004 (P < 0·001)[26]. The authors speculate that the increase in thinness might be due to earlier sexual maturation, greater participation in sports and keener concern about controlling body weight in children.

We also found a significant association between childhood obesity and adult MetS in men (OR = 4·66, 95 % CI 1·40, 15·51) after adjusting for age and BMI at baseline, which corroborates findings in other studies[27,28]. It has been shown that overweight and obese children and adolescents are more likely to become obese adults[28]. Excess body fat, especially visceral fat, is a fundamental component of MetS[1,8].

Regarding the absence of association for the female sex, this could be explained because of the lower percentage of women who were diagnosed with MetS during follow-up. Therefore, our cohort might be underpowered to assess these associations among women.

Our study has some limitations. Childhood and adolescence/young adulthood body weight was not directly measured but self-reported. The assessment was based on recalled body shape of the participants at ages 5 and 20 years.

Moreover, 69 % of our study participants classified themselves as underweight at age 5 years. In respect of

this fact, we have to add a cautionary comment because a 30-year recollection of body shape as a surrogate for BMI is likely to be associated with a sizeable degree of measurement error. However, the validity of the remote recall of body shape has been demonstrated and the potential bias would be more likely towards the null value[14]. The MetS components were also not measured directly. However, these self-reported components by participants of the SUN Project were validated in specific study[18]. Furthermore, >45% of our participants were health professionals. As a consequence, their self-reported information is likely to be of better quality than that other studies based on self-report[29].

An additional limitation in our study is related to possible unmeasured confounders, since we adjusted only for age and adult BMI. The lack of control for potential confounders also invites caution in the interpretation of our findings. However, adjustment for potential important known confounders did not substantially change the observations from the crude analysis; and even those changes were away from the null. Therefore, we do not consider residual confounding as the most likely explanation for our results.

Some strengths of the present study are its prospective design, the inclusion of a high number of participants, and a long-term follow-up enabling us to assume a sufficiently large induction period and to avoid reverse causation.

Conclusions

In summary, childhood underweight and weight gain during childhood to adolescence/young adulthood increased the chance of adult MetS development among men. These results, if causal and confirmed in other prospective studies, support treating childhood underweight and weight gain during childhood to adolescence/young adulthood among men as part of comprehensive adult MetS prevention efforts.

Acknowledgements

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