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ARTICLE

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Early determinants of metabolically healthy obesity in young adults: study of the Northern Finland Birth Cohort 1966

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Abstract

Background A body of literature suggests a metabolically healthy phenotype in individuals with obesity. Despite important clinical implications, the early origins of metabolically healthy obesity (MHO) have received little attention.

Objective To assess the prevalence of MHO among the Northern Finland Birth Cohort 1966 (NFBC1966) at 31 years of age, examine its determinants in early life taking into account the sex specificity.

Methods We studied 3205 term-born cohort participants with data available for cardio-metabolic health outcomes at 31 years, and longitudinal height and weight data. After stratifying the population by sex, adult BMI and a strict definition of metabolic health (i.e., no risk factors meaning metabolic health), we obtained six groups. Repeated childhood height and weight measures were used to model early growth and early adiposity phenotypes. We employed marginal means adjusted for mother and child covariates including socio-economic status, birth weight and gestational-age, to compare differences between the groups.

Results The prevalence of adult MHO was 6% in men and 13.5% in women. Differences in adult metabolic status were linked to alterations in BMI and age at adiposity peak in infancy ($p < 0.0003$ in men and $p = 0.027$ in women), and BMI and age at adiposity rebound (AR) ($p < 0.0001$ irrespective of sex). Compared to MHO, metabolically unhealthy obese (MUO) women were five and a half months younger at AR ($p = 0.007$) with a higher BMI while MUO men were four months older ($p = 0.036$) with no difference in BMI at AR.

Conclusion At the time of AR, MHO women appeared to be older than their MUO counterparts while MHO men were younger. These original results support potential risk factors at the time of adiposity rebound linked to metabolic health in adulthood. These variations by sex warrant independent replication.

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Introduction

The prevalence of obesity nearly tripled worldwide over the past 40 years. In 2016, 650 million adults were obese, representing 13% of the world's adult population [1]. This epidemic represents a major public health concern and an economic threat. Obesity is an important risk factor for common metabolic disorders, low-grade inflammation and clinical end-points such as hypertension, insulin resistance (IR), type 2 diabetes (T2D), cardiovascular diseases (CVD) and several types of cancers [2, 3]. However, there are indications [4, 5] that a subgroup of obese individuals could be protected from the typical obesity-associated disorders such as hypertension, dyslipidaemia and impaired glucose metabolism despite having large quantities of fat mass. They have been identified as metabolically healthy obese (MHO) [6, 7]. The prevalence of MHO varies significantly between studies. Besides study specificities (e.g., age, ethnicity), the main reason for the observed differences would probably be lack of a unified definition of metabolic health and obesity. Many definitions coexist; one of the most frequent relies on the absence of metabolic syndrome. Others include favorable inflammatory profile or insulin sensitivity or use waist circumference or body fat percentage instead of standard BMI [8].

It is unclear whether the MHO phenotype associates with decreased or delayed mortality and morbidity risks compared to metabolically unhealthy obese (MUO) or metabolically healthy non-obese subjects. Overall, the evidence between-group comparisons is contradictory, questioning its clinical and public health relevance. Some studies suggest that MHO individuals are not at increased risk of mortality, T2D, cardiovascular events, all-cause cancers or thicker carotid intima-media, when compared to metabolically healthy non-obese individuals [9–12] while the Whitehall [13] and Pizarra studies [14] both suggest that MHO individuals were at a lower risk of developing T2D when compared to MUO. However, the analysis of the NHANES III study [15] showed an increase in all-cause mortality in obese individuals regardless of their metabolic health, and Chang and colleagues [16] found an increased risk of Non-Alcoholic Fatty Liver Disease (NASH) linked to adiposity. Most studies investigating MHO apply to adult populations but only a few cover the period from infancy into adulthood [17] despite the established evidence that early growth factors such as birth weight, timing of adiposity rebound and changes in linear growth have been linked to obesity in adult life [18, 19]. Moreover, differences in growth exist between males and females starting as early as in-utero with boys generally having a higher birth weight, a later adiposity rebound and a later puberty than girls [20]. Differences by sex carry on in adulthood with men tending to have more abdominal fat than women among other metabolic adversities. We therefore hypothesized that early life factors, notably the timing of adiposity rebound are linked with MHO in adulthood. The aim of this study was threefold, (i) assess the prevalence of MHO among the Northern Finland Birth Cohort 1966 (NFBC1966) at 31 years of age, (ii) examine the early life origins of MHO and (iii) characterise sex specificity.

Material and methods

Population studied

We analysed the NFBC1966 data until the age of 31 years. Pregnant women from the two northernmost provinces of Finland with expected delivery during the year 1966 were enrolled. The cohort includes 96% of all births in the area with 12 058 live born. During infancy and childhood, the Child Health and Welfare nurses recorded multiple and regular growth measures. At 31 years of age, questionnaires about health and lifestyle were sent to all cohort members whose address was known. Due to the data collection logistics, only those living in Northern Finland (Lapland and Oulu provinces) or Helsinki area were invited to participate in a clinical examination. This subpopulation represents well the whole study population [21].

We excluded participants without fasting blood sample, pregnant women and participants with congenital history of CVD. Following Wildman's definition, we excluded individuals with a BMI under 18.5 kg/m^2, underweight individuals being more prone to adverse health outcomes. We also excluded twins, pre-term (<37 gestational weeks) and post-term (>42 gestational weeks) to reduce confounding by gestational age or otherwise deviant intrauterine growth and those without data available for adiposity peak (AP) or adiposity rebound (AR). The present study includes only participants with complete metabolic data (blood pressure, triglycerides, HDL-cholesterol, fasting glucose, high sensitivity C-Reactive Protein (hsCRP) and HOMA-IR), AP and AR data. Figure 1 shows the flow chart of the study; the remaining 3205 cohort members were included in further analyses (52.0% men). The Ethics Committee of the Northern Ostrobothnia Hospital District approved the study and the study participants signed a written inform consent.

Study variables

Questionnaire at 31 years

The cohort members completed a postal questionnaire about health, lifestyle and socio-economic position. Smoking habits were categorized as non-smoker and smoker, alcohol consumption was estimated in grams per day. Diet score

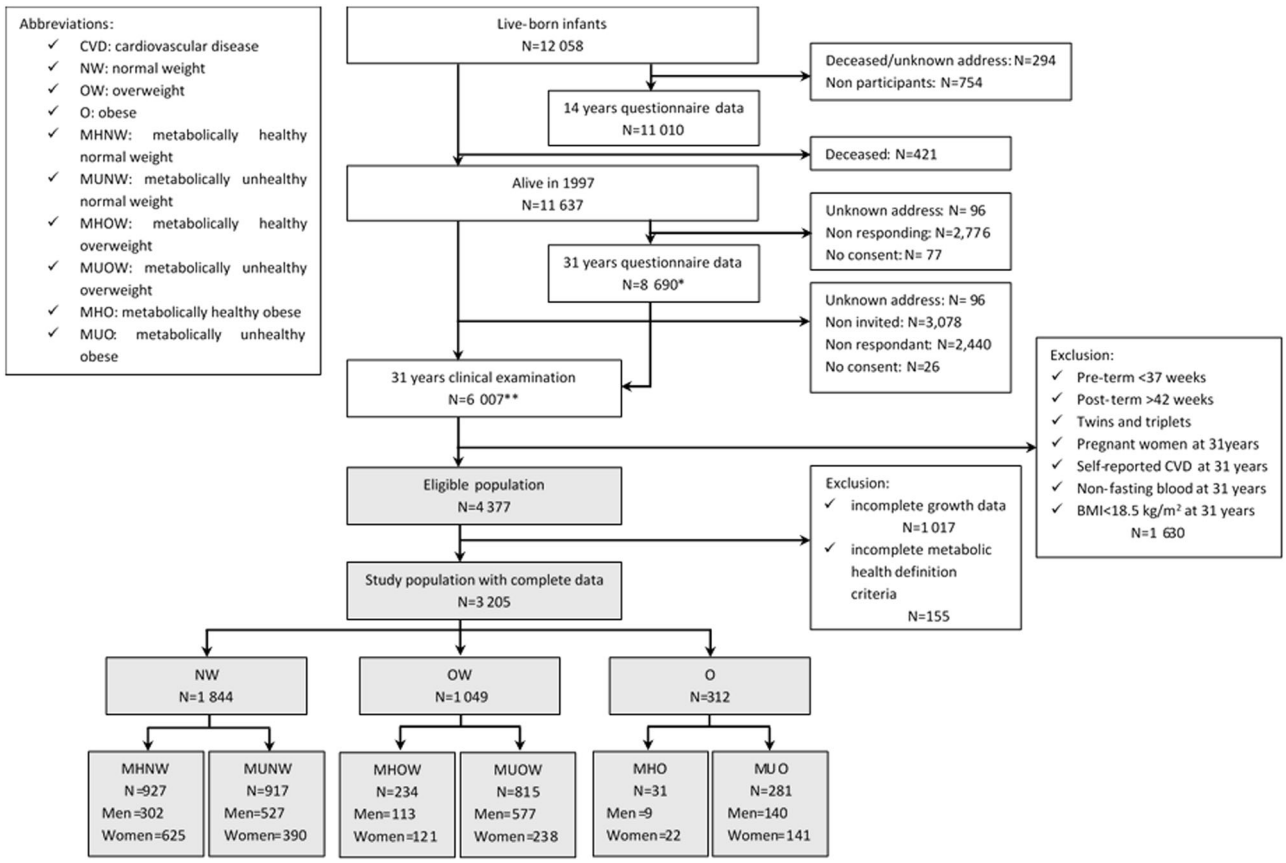

Fig. 1 Flow chart of the NFBC1966 data collection process and sampling of the metabolically healthy obesity study. *Two cohort members outside postal questionnaire target also responded. **Ten cohort members outside clinical examination target also participated

included the frequency of consumption of food rich in fibre and food high in saturated fat and was coded previously [22]. A score of three or less determined a healthy diet whereas four or five indicated an unhealthy diet.

Light physical activity was defined as physical activity causing no sweating or shortness of breath and brisk physical activity causing at least sweating and shortness of breath. Using the duration and intensity of brisk/light physical activity, we calculated Metabolic Equivalent of Task (MET) minutes per week. The socioeconomic status was based on occupation and employment status and categorized as professionals, skilled workers, unskilled workers, farmers and others (students, pensioners, long-term unemployed or not defined). Self-reported medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [23].

Clinical examination at 31 years of age

Trained research nurses performed the anthropometric measurements, carried out the medical examinations and supervised the fitness tests. Weight (kg), height (cm), waist circumference (cm) (midway between the lowest rib margin and the iliac crest), hip circumference (cm) (at the widest trochanters) were measured. The BMI (kg/m^2) and the waist/hip ratio (WHR) were calculated. Two measures of systolic and diastolic blood pressure were taken in a sitting position using a standard mercury sphygmomanometer after a 15 min rest. We used the average of the readings.

Muscular fitness was assessed by trunk extension test and maximal isometric hand grip test. The trunk extension test involved the subject holding a prone position with the lower body lying on the stand and the upper body unsupported as long as possible with a maximum of four minutes. The maximal isometric handgrip was performed three times on the dominant hand; the highest value of the three trials was reported as a result. The detailed procedures of these tests have been previously described [24].

Cardiorespiratory function and fitness were evaluated using spirometry test and step test described earlier in details in NFBC1966 studies [25]. Respiratory function was measured by forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). The test was performed three times and the highest FEV1 and FVC measurements were used to calculate FEV% (FEV1/FVC ratio). The submaximal four-minute single step test was conducted

without shoes on a bench 33 cm high for the females and 40 cm high for the males, the heart rate was measured after the test.

Biochemical measures

Blood samples at the age 31 years were drawn after overnight fasting, the methods have been reported in previous studies [26]. The samples were aliquoted either as whole blood, kept at 4 °C to be analysed on the same day for glucose by a glucose dehydrogenase method (Granutest 250, diagnostic Merck, Germany) or processed according to standard protocols to acquire plasma and serum. The serum was kept at −20 °C until further analysis. Serum insulin concentrations were measured within seven days by radioimmunoassay (Pharmacia Diagnosis, Sweden). The lipid blood samples (stored at −80 °C) were analysed by enzymatic assays using Hitachi 911 automatic analyser and commercial reagents (Roche, Manheim, Germany) in the accredited laboratory of the Oulu University Hospital. Serum high sensitivity C-reactive protein (hs-CRP) concentrations were analysed by immunoenzymometric assay (Medix Biochemica, Espoo, Finland). The insulin sensitivity was determined using the Homeostatic Model Assessment based Insulin Resistance (HOMA-IR), derived from the following ((glucose (mmol/l)×insulin (mmol/l))/22.5).

Metabolic Health Status

The metabolic health status was defined using a selection of cardio-metabolic and inflammation (proxy: hsCRP) criteria proposed by Wildman and colleagues:[6]

- Elevated blood pressure (≥130 or ≥85 mmHg) or antihypertensive medication (ATC codes: C02, C03, C07, C08, C09).
- Fasting hypertriglyceridemia (≥1.70 mmol/l).
- Fasting low HDL-cholesterol level (< 1.04 mmol/l for men and < 1.30 mmol/l for women) or lipid-lowering medication (ATC codes: B04, C10).
- Elevated fasting plasma glucose (≥5.55 mmol/l) or diabetes medication (ATC codes: A10).
- Elevated HOMA-IR (>90th percentile value, i.e., 1.66 for men and 1.52 for women).
- Elevated hsCRP level (>90th percentile value, i.e., 3.50 for men and 5.40 for women).

Wildman and colleagues determine cardio-metabolic health by the presence of zero or one criteria. In the present analysis we opted for a strict definition of cardio-metabolic health; individuals being cardio-metabolically healthy in the absence of any of the criteria mentioned above. The participants were then stratified according to their BMI as normal weight (18.5 kg/m^2≤BMI<25 kg/m^2), over-weight (25 kg/m^2≤BMI<30 kg/m^2) and obese (BMI≥30 kg/m^2). The six groups resulting from this categorisation were called: metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight (MHOW), metabolically unhealthy overweight (MUOW), metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO).

Wildman and colleagues did not exclude elevated hsCRP values; hsCRP ≥10 mg/l is commonly used as a threshold for acute inflammation. A sensitivity analyse did not show any differences between inclusion and exclusion of individuals with elevated hsCRP ($N = 116$) or self-reported fever at the time of the clinical examination ($N = 13$). We kept these individuals in the analyses, following Wildman's definition.

Growth variables

Birth weight (kg) and birth length (cm) were measured using standard methods of care. Gestational age was calculated from the mother's last menstrual period. In order to model the BMI curve, described in detail elsewhere [27], two growth periods were considered; infancy (from two weeks to 18 months) and childhood (from 18 months to 13 years) [28]. Individuals with fewer than three measurements in each period were excluded. A BMI growth model was fitted to these data, identifying the AP, usually timed around 9 months of age and the AR, at the nadir of the curve generally occurring between 5 and 7 years. Peak height (PHV in cm/month) and peak weight velocity (PWV in kg/month) in infancy were derived from sex stratified non-linear mixed effect Reed1 models, previously described elsewhere [29].

Early life related covariates

These variables were retrieved from questionnaires filled in by mothers during pregnancy at maternity clinics. Maternal smoking at two months pregnancy was categorised as no smoker, former smoker and smoker, wantedness of pregnancy as wanted, mistimed or unwanted, and the marital status of the mother as married, unmarried, widowed or divorced. Social class at birth was assessed by the prestige of father's occupation: no occupation, professionals and white collar upper level, white collar lower level, blue collar and farmers. The mother's education ranged from no education to beyond matriculation examination. We also included continuous variables such as parity, age of mother, birth weight, gestational age, and mother's BMI before pregnancy in the model.

Table 1 Characteristics of metabolic health status in NFBC1966

	Metabolically healthy		Metabolically Unhealthy		
	N	Mean ± SD (%)	*N*	Mean ± SD (%)	*p* value
Gender	1192		2013		<0.0001
Male	424	35.6	1244	61.8	
Female	768	64.4	769	38.2	
Weight, kg	1192	66.5 ± 11.0	2013	78.0 ± 14.9	<0.0001
BMI, kg/m^2	1192	23.1 ± 2.9	2013	26.0 ± 4.4	<0.0001
BMI categories	1192		2013		<0.0001
Normal weight	927	77.8	917	45.5	
Overweight	234	19.6	815	40.5	
Obese	31	2.6	281	14.0	
Waist circumference, cm	1188	78.7 ± 9.1	2005	87.9 ± 12.1	<0.0001
Waist-to-hip ratio	1187	0.83 ± 0.08	2005	0.88 ± 0.08	<0.0001
SES	1181		1999		<0.0001
1: Professional	297	25.1	471	23.6	
2: Skilled worker	408	34.5	554	27.7	
3: Unskilled worker	257	21.8	592	29.6	
4: Farmer	34	2.9	65	3.2	
5: Other	185	15.7	317	15.9	
Smoking	1179		1994		0.0480
No smoker	523	44.4	813	40.8	
Smoker	656	55.6	1181	59.2	
Alcohol consumption, g/day	1159	7.5 ± 13.5	1967	11.0 ± 17.4	<0.0001
Unhealthy diet score	1187		2002		0.0074
Healthy	1072	90.3	1745	87.2	
Unhealthy	115	9.7	257	12.8	
Physical activity (light), min/week	1159	468.1 ± 480.1	1980	444.7 ± 494.3	0.058
Physical activity (brisk), min/week	1177	452.8 ± 537.3	2000	452.5 ± 560.9	0.83
Max handgrip, kg	1175	35.5 ± 12.3	1976	41.4 ± 13.1	<0.0001
Step test, heart beats/min	1146	144.9 ± 17.0	1882	150.5 ± 16.9	<0.0001
Back endurance test, seconds	1160	298.8 ± 93.6	1929	253.1 ± 98.6	<0.0001
Fev1/Fvc ratio	1177	0.84 ± 0.07	1982	0.84 ± 0.06	0.13
Insulin, ulU/ml	1192	6.91 ± 1.75	2013	9.42 ± 4.63	<0.0001
Cardio-metabolic factors					
SBP, mmHg	1192	116.4 ± 7.9	2013	131.2 ± 12.8	<0.0001
DBP, mmHg	1192	71.6 ± 7.7	2013	82.0 ± 11.2	<0.0001
HDL cholesterol, mmol/l	1192	1.68 ± 0.33	2013	1.45 ± 0.37	<0.0001
Triglycerides, mmol/l	1192	0.87 ± 0.30	2013	1.38 ± 0.83	<0.0001
Glucose, mmol/l	1192	4.86 ± 0.34	2013	5.15 ± 0.55	<0.0001
HOMA-IR	1192	0.89 ± 0.23	2013	1.23 ± 0.59	<0.0001
High-sensitivity C-reactive protein, mg/l (90th)	1192	0.83 ± 0.93	2013	2.58 ± 4.44	<0.0001

BMI body mass index, *SES* socio-economic status, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high density lipoprotein, *HOMA-IR* homeostasis model assessment of insulin resistance

Statistical analysis

We conducted statistical analyses using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina). Due to the divergences in their physiology and development, all analyses were done separately for men and women [30]. For sensitivity analyses we excluded oral contraceptive (OCPs) users, as OCPs are known to have an impact on women's

cardio-metabolic health [30]. This, however, did not affects. We excluded 1017 cases of incomplete growth data. We compared the distributions of complete and incomplete cases by the cardio-metabolic groups and found no difference (data not shown).

The descriptive statistics are presented as mean values (with standard deviations, SDs) for continuous variables and percentages for categorical variables. Variables with non parametric distributions were log-transformed. The differences between the groups were tested with ANOVA. We performed comparisons of marginal means (LS-means) between the reference and the other groups using Dunnett's adjustment for multiple testing. We calculated effect sizes using partial omega squared and the results were interpreted as percentage difference between the groups. For theses analyses, we used MHO as a reference. A p value below 0.05 denotes statistical significance.

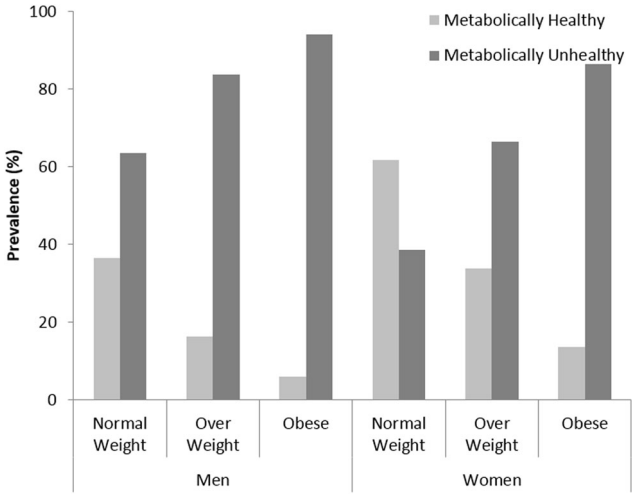

Fig. 2 Prevalence of metabolic phenotypes amongst NFBC1966 by their BMI categories (normal weight, overweight and obese) and sex. NW Normal Weight, OW Overweight, O Obese, MH Metabolically Healthy, MU Metabolically Unhealthy

Results

Table 1 shows the demographic and clinical characteristics of the study population by their cardio-metabolic health status. At the age of 31 years of age, 37.2% of the subjects overall were metabolically healthy. This metabolically healthy group contains half of all women and a quarter of all men.

Prevalence of metabolically healthy obesity

Individuals in the metabolically healthy group were less obese than in the metabolically unhealthy group (respectively 2.6% vs 14.0%). They had also a smaller waist circumference. We observed a smaller proportion of unskilled workers and a greater proportion of skilled workers in the metabolically healthy group in comparison to the metabolically unhealthy group. The metabolically healthy group also reported less smoking and drinking, a healthier diet and showed better fitness (step test and back endurance test) than the metabolically unhealthy phenotype.

Figure 2 illustrates the proportions of the different metabolically healthy (MH) and unhealthy (MUH) groups stratified by categories of BMI (normal weight, overweight, obese) and sex at 31 years. The proportion of MH persons decreases in a stepwise manner with increasing BMI categories in both sexes, with women being metabolically healthier in proportion.

Early life determinants

Tables 2a and 2b show the distribution of the early growth parameters in men and women by their metabolic health status and BMI categories at 31 years of age. In men, there was a large difference in birth weight between MUNW group which had the lowest birth weight (3552 (483 SD) grams) and MHOW with the highest (3682 (490 SD) grams) of all groups ($p = 0.035$). In the women's group, MUNW also tended to be the lightest at birth with an average birth weight of 3 446 (435 SD) grams and MHO were the heaviest (3581 (390 SD) grams) ($p = 0.15$). Of all groups, MHO men had the highest BMI at AP, 18.6 (0.84 SD) kg/m^2 ($p = 0.0003$). In men, MHO were the first to experience AR at four years and seven months, followed by MUO, MHOW, MUOW, MHNW and finally MUNW who rebounded more than seventeen months later ($p < 0.0001$; Table 2a). In contrast, MUO women were the first to rebound at four years and four months of age, followed by MHO, MHOW, MUOW, MHNW and MUNW, seventeen months later ($p < 0.0001$; Table 2b), i.e., overweight and obese subjects had rebounded earlier than normal weight subjects. At the time of adiposity rebound, MHO men and MUO women had the highest BMI of all groups with 16.5 (1.0 SD) kg/m^2 and 16.1 (1.1 SD) kg/m^2 respectively.

Figure 3 demonstrates the marginal mean differences for age (3A) and BMI (3B) at AR between metabolic groups using the MHO as a reference. In Fig. 3a, we observed clusters of metabolic groups by the BMI categories. There were significant differences between MHO men and the other groups but the effect sizes were weak in that AR explained around 2% of the variance between MHO and MUNW, as well as between MHO and MHNW. The women showed a similar trend in the BMI clustering described in men except for the obese subgroup where, contrary to men, MUO rebounded earlier than MHO ($p = 0.0364$). The effects sizes were also small in the female groups.

Table 2a Early life characteristics of men in NFBC1966 according to BMI categories and metabolic health status

	Normal weight				Overweight				Obese				
	Metabolically healthy		Metabolically unhealthy		Metabolically healthy		Metabolically unhealthy		Metabolically healthy		Metabolically unhealthy		
	N	Mean ± SD (%)	*N*	Mean ± SD (%)	*N*	Mean ± SD (%)	*N*	Mean ± SD (%)	*N*	Mean ± SD (%)	*N*	Mean ± SD (%)	*p* value
Gender													
Male	302		527		113		577		9		140		<0.0001
Birth data													
Birth weight, grams	302	3650 ± 531	527	3552 ± 483	113	3682 ± 490	577	3589 ± 483	9	3672 ± 336	140	3624 ± 531	0.0352
Birth length, cm	300	51.0 ± 1.9	525	50.7 ± 2.0	112	51.1 ± 1.9	573	50.9 ± 1.9	9	50.8 ± 1.3	138	51.0 ± 2.1	0.12
Ponderal index, g/cm^3	300	2.74 ± 0.26	525	2.72 ± 0.23	112	2.75 ± 0.25	573	2.72 ± 0.23	9	2.80 ± 0.19	138	2.73 ± 0.23	0.61
Gestational age at birth, weeks	302	40.2 ± 1.3	527	40.0 ± 1.4	113	40.2 ± 1.2	577	40.1 ± 1.3	9	40.7 ± 1.0	140	40.4 ± 1.1	0.0219
Growth													
Peak height velocity in infancy, cm/month	270	4.36 ± 0.25	475	4.39 ± 0.23	99	4.38 ± 0.22	519	4.39 ± 0.24	9	4.28 ± 0.23	126	4.39 ± 0.25	0.42
Peak weight velocity in infancy, kg/month	271	1.11 ± 0.12	476	1.10 ± 0.13	99	1.14 ± 0.14	520	1.13 ± 0.14	9	1.15 ± 0.15	126	1.16 ± 0.14	<0.0001
Adiposity peak													
BMI, kg/m^2	233	18.2 ± 0.8	431	18.1 ± 0.7	89	18.3 ± 0.8	459	18.2 ± 0.8	9	18.6 ± 0.8	110	18.4 ± 0.8	0.0003
Age, years	233	0.75 ± 0.03	431	0.76 ± 0.03	89	0.76 ± 0.03	459	0.76 ± 0.03	9	0.77 ± 0.03	110	0.76 ± 0.04	0.14
Adiposity rebound													
BMI, kg/m^2	296	15.2 ± 0.8	525	15.1 ± 0.8	113	15.8 ± 0.9	572	15.6 ± 0.9	9	16.5 ± 1.0	140	16.3 ± 1.1	<0.0001
Age, years	296	5.94 ± 0.67	525	6.06 ± 0.67	113	5.42 ± 0.69	572	5.52 ± 0.74	9	4.62 ± 1.05	140	4.97 ± 0.89	<0.0001

Figure 3b shows the differences in BMI at AR between MHO and other metabolic groups. In men, we noticed again clusters by the BMI categories There was no significant difference between MHO and MUO and between MHO and MHOW. In women, there was no difference between MHO and the overweight subgroups except a nominally significant difference between MHO and MUO ($p = 0.040$) with small effect size.

Discussion

The present analysis supports the evidence of a link between early timing and BMI at adiposity rebound and the metabolically healthy obesity phenotype in adult men.

In our study, we observed that 41.4% of men and 23.3% of women at the age of 31 years were overweight and 8.9% of men and 10.6% of women were obese, which was consistent with national statistics at the time in Finland [31]. Within the obese population studied, we found that only 6.0% of men and 13.5% of women were metabolically healthy by strict criteria. The higher prevalence of MHO in women over men is in accordance with other studies [7, 32]. Our findings also support earlier studies from this cohort [28] where categorisation, according to metabolic health in BMI classes, suggested sex specificity in the growth patterns.

Numerous definitions of metabolic health coexist in the literature, leading to a large variation in the prevalence of MHO [7, 33]. Even when using the same definition, the Bioshare-EU project observed substantial variability with 10–40%, in the prevalence of MHO in several European cohorts [5]. We chose to use a more stringent definition of MHO according to Wildman [6], namely zero out of six criteria needed to qualify as metabolically healthy. This decision was made based on the relative young age and the inherent high blood pressure of our population. Indeed, 57.8% of men and 29.7% of women had a blood pressure greater than 130/85 or were using anti-hypertension medication. Critically, high blood pressure is endemic in Finland although global efforts have been made to tackle it. In the early 1970s the country had the highest prevalence of hypertension and coronary heart disease mortality in the world [34]. After 35 years, health policies exemplified by the North Karelia project [34] have been effective in influencing health behaviour and dietary habits in order to

Table 2b Early life characteristics of women in NFBC1966 according to BMI categories and metabolic health status

	Normal weight				Overweight				Obese				
	Metabolically healthy		Metabolically unhealthy		Metabolically healthy		Metabolically unhealthy		Metabolically healthy		Metabolically unhealthy		
	N	Mean ± SD (%)	*N*	Mean ± SD (%)	*N*	Mean ± SD (%)	*N*	Mean ± SD (%)	*N*	Mean ± SD (%)	*N*	Mean ± SD (%)	*p* value
Gender													
Female	625		390		121		238		22		141		<0.0001
Birth data													
Birth weight, grams	625	3471 ± 465	390	3446 ± 435	121	3564 ± 451	238	3 479 ± 492	22	3 581 ± 390	141	3 514 ± 451	0.15
Birth length, cm	616	50.1 ± 1.9	386	50.0 ± 1.8	120	50.1 ± 1.8	234	50.0 ± 1.9	22	50.2 ± 1.6	139	50.0 ± 2.0	0.80
Ponderal index, g/cm^3	616	2.75 ± 0.24	386	2.75 ± 0.22	120	2.82 ± 0.27	234	2.78 ± 0.24	22	2.83 ± 0.23	139	2.83 ± 0.47	0.0022
Gestational age at birth, weeks	625	40.2 ± 1.2	390	40.2 ± 1.2	121	40.4 ± 1.3	238	40.1 ± 1.3	22	39.8 ± 1.7	141	40.1 ± 1.3	0.12
Growth													
Peak height velocity in infancy, cm/month	568	4.03 ± 0.28	350	4.02 ± 0.27	109	3.99 ± 0.27	211	4.03 ± 0.25	20	4.09 ± 0.27	126	4.05 ± 0.31	0.53
Peak weight velocity in infancy, kg/month	570	1.00 ± 0.13	353	1.00 ± 0.12	109	1.01 ± 0.14	211	1.02 ± 0.12	20	1.05 ± 0.14	126	1.02 ± 0.14	0.12
Adiposity peak													
BMI, kg/m^2	514	17.7 ± 0.8	312	17.7 ± 0.7	96	17.9 ± 1.0	192	17.9 ± 0.8	15	17.9 ± 0.6	111	17.9 ± 0.9	0.0268
Age, years	514	0.76 ± 0.04	312	0.76 ± 0.03	96	0.76 ± 0.03	192	0.76 ± 0.03	15	0.76 ± 0.04	111	0.76 ± 0.03	0.69
Adiposity rebound													
BMI, kg/m^2	621	15.1 ± 0.9	389	15.0 ± 0.9	121	15.9 ± 1.2	234	15.6 ± 0.9	21	16.1 ± 1.1	141	16.4 ± 1.4	<0.0001
Age, years	621	5.77 ± 0.72	389	5.83 ± 0.74	121	5.01 ± 0.84	234	5.31 ± 0.76	21	4.66 ± 1.05	141	4.37 ± 0.94	<0.0001

achieve an 80% decline in the coronary mortality in Finland. Yet, mean blood pressure remains high and the current hypertension threshold for Finland is equal or greater than 140/90 [35].

Thirty years ago, Rolland-Cachera and colleagues [36] identified early adiposity rebound as a predictor of adult obesity; this has been corroborated by many studies since [37–39]. Adiposity rebound is defined as the nadir of the BMI growth after which BMI starts to rise again and it normally occurs between five and seven years of age in the western countries. The typical pattern associated with early adiposity rebound is low BMI at time of rebound and subsequent increase [40–42]. A shift in the BMI growth curve seems to have happened in the early seventies and younger cohorts show adiposity rebound happening earlier. This pattern is now characteristic of children born during the obesity epidemic [42], which NFBC1966 is pre-dating. In the model developed in this study, we did not see a low BMI at time of the rebound for the obese adults, but we observed that both obese men and women had a higher BMI at rebound than in the other groups. Nevertheless, consistently with previous findings [43, 44], we found a negative association between age at adiposity rebound and adult BMI after stratifying by sex and BMI. It confirms earlier studies on NFBC1966 showing that an earlier adiposity rebound was a risk factor for an adverse cardiometabolic profile, independently of BMI at the time of rebound [28]. However, our findings regarding MHO men tend to contrast with the general hypothesis that an earlier age at adiposity rebound would predict an unhealthy metabolic phenotype. Our results showed that MHO men rebounded earlier than their unhealthy counterparts. In contrast, the earlier obese women rebounded, the more likely they seemed to become metabolically unhealthy in adulthood.

It seems that two main early patterns lead to obesity, tracking and catching up. The first one involves infants with high birth weight who gained weight between birth and two years, a predictor of later insulin sensitivity [19]. These children with obesity display high BMI at all ages, reflecting both lean and fat mass, showing some protection from central obesity and IR; the authors suggested that an always-high BMI could correspond to MHO [45]. The second pattern involves low birth weight babies who

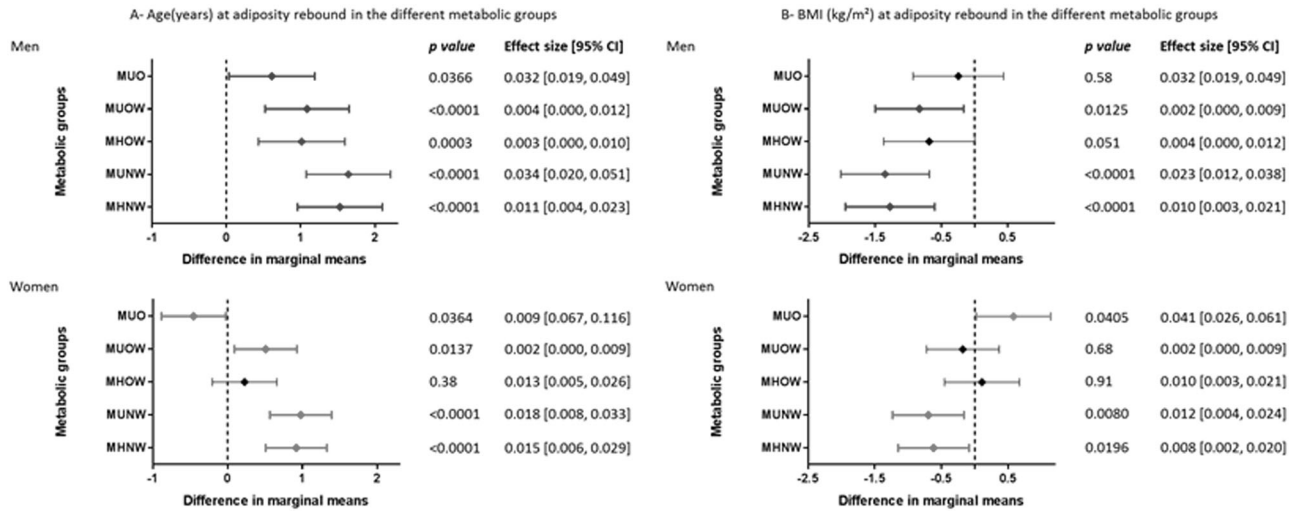

Fig. 3 Forest plots showing differences in marginal means (95% CI) of age at adiposity rebound (years) **a**, between each group and the MHO reference group (vertical dotted line). The effect size is presented as partial omega squared. **b** shows the corresponding results for BMI at adiposity rebound. This model is adjusted for birth weight, gestational age, mother's age, mother's BMI, mother's marital status, child wantedness, parity, mother's smoking at 2 months of pregnancy, mother's education, father's occupation. MUO Metabolically Unhealthy Obese, MUOW Metabolically Unhealthy Overweight, MHOW Metabolically Healthy Overweight, MUNW Metabolically Unhealthy Normal Weight, MHNW Metabolically Healthy Normal Weight

underwent a rapid catch-up growth in early life. This process depletes the infant's fat stores, triggering an early adiposity rebound, subsequently followed by an increase in BMI consisting in the deposition of fat rather than lean mass [45]. In the Flame Study in New Zealand, no differences were found in anthropometry measures and body composition at three years between early and late rebounders except that boys with early AR showed more fat free mass than the late rebounders [46]. At seven years old, marked differences appeared. The early rebounder boys were no taller but heavier with greater BMI than their late counterparts and they showed a greater deposition of fat free mass than fat mass. As for girls, early rebounders were not taller but gained considerably more weight, most of it consisting of fat mass with a small contribution from fat free mass. In another study involving young Swedish boys, early adiposity rebound was associated with higher fat mass, consisting of subcutaneous fat but not of visceral fat [38]. Visceral fat has been associated with unhealthy metabolic status in adulthood and subcutaneous fat with metabolically healthy status [47]. Unfortunately, adiposity data during childhood or at 31 years old in NFBC1966 is not available to replicate this analysis on MHO subpopulation.

Results from the present study reinforce evidence of the role of age at AR as a risk factor for obesity. Although adiposity rebound might be a good marker for later obesity, it could only capture the consequences of previous events, thus earlier steps in infancy are to be considered. The period from birth to two years old appears to be a key period in adult obesity [19]. However, our study did not provide evidence of further link between adult metabolic health and early growth factors preceding adiposity rebound. Earlier studies with NFBC1966 data revealed that low birth weight and rapid infant growth are important determinants of adult blood pressure [21]. Early adiposity rebound was robustly associated with the components of the metabolic syndrome irrespective of sex and adult BMI [28], and according to the authors, an important change in BMI after AR could predict an adverse cardio-metabolic profile in adulthood. In the 1982 Pelotas birth cohort study, a rapid postnatal weight gain after the age of two induced greater adult visceral fat, which was accentuated in low birth weight babies [18]. In addition, Salonen et al. [48] showed that slow weight gain from 0 to 2 years would increase the risk of developing metabolic syndrome in the obese adults. Similarly, they showed that the first six months after birth might be a crucial period in link to impaired glucose tolerance [49].

Strengths and limitations

This study shows important strengths. To our knowledge, this is the first study to show an association between the timing of adiposity rebound and MHO later in adult men. Furthermore, NFBC1966 is a homogeneous birth cohort with detailed reliable data on childhood growth. A limitation of our study was the low number of obese individuals in NFBC1966 at the age of 31 years which leads to the low prevalence of strictly MHO men and women. This was even more pertinent in men and it might have an influence on the statistical power of the study. Another possible limitation is the attrition due to the constraints associated with the BMI growth model and resulting in the exclusion of individuals

with missing growth data. However, we did not find any difference between complete and incomplete cases groups that could indicate a bias in the analysis. Another aspect to consider is that NFBC1966 is a pre-obesity epidemic cohort; the participants were children in the early seventies, at a time where child obesity was not so common.

Conclusion

In conclusion, consistently with others, we observed a subpopulation of MHO individuals in NFBC1966. The present study establishes a possible link between early age at adiposity rebound and a favourable metabolic health status in term-born obese adult men, suggesting that MHO finds its roots in early childhood and emphasizing the sex difference in the pathways leading to metabolic health later in life. Further longitudinal studies in larger populations are warranted for a better understanding of this concept. Life-course perspective is paramount in the understanding of the development of obesity and non-communicable diseases, and furthermore, prenatal and childhood growth data are equally essential as adult data.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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