# Increase in adiposity from childhood to adulthood predicts a metabolically obese phenotype in normal-weight adults

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**Abstract**

Normal-weight is associated with a favorable cardiometabolic risk profile and low risk of type 2 diabetes and cardiovascular disease. However, some normal-weight individuals – the "metabolically obese normal weight" (MONW) – show a cardiometabolic risk profile similar to the obese. Previous studies have shown that older age, central body fat distribution, and unfavourable lifestyle increase the risk of MONW. However, the role of early-life factors in MONW remains unknown. We examined the associations of early-life factors with adult MONW in 1 178 individuals from the Cardiovascular Risk in Young Finns study who were followed up from childhood to adulthood. The strongest early predictor for adult MONW was an increase in BMI from childhood to adulthood ($p=3.1x10^{-11}$); each 1 SD increase in BMI z-score from childhood to adulthood led to a 2.56-fold increase in the risk of adult MONW (CI95%=1.94-3.38). Other significant predictors of adult MONW were male sex (OR=2.38, 95%=1.63-3.47, $p=7.0x10^{-6}$), higher childhood LDL cholesterol (OR=1.41 per 1 SD increase in LDL cholesterol, CI95%=1.14-1.73, p=0.001), and lower HDL cholesterol (OR=1.51 per 1 SD decrease in HDL cholesterol, CI95%=1.23-1.85, $p=5.4x10^{-5}$). Our results suggest that an increase in adiposity from childhood to adulthood is detrimental to cardiometabolic health, even among individuals remaining normal weight.

## Introduction

Normal weight (BMI 18.5-25 kg/m$^2$) is associated with a healthy cardiometabolic risk profile and a low risk of type 2 diabetes and cardiovascular disease (1). However, some individuals with normal weight – the "metabolically obese normal-weight" (MONW) – show a cardiometabolic risk profile similar to the obese (2). Individuals with MONW have a three-fold higher risk of cardiovascular events and all-cause mortality compared to normal weight individuals with a normal metabolic profile (3)**.** Thus, it is important to understand the underlying risk factors and mechanisms**.**

Previous studies have found that male sex, older age, central body fat distribution, physical inactivity, smoking, and high alcohol consumption, are associated with the MONW phenotype in adults (4, 5). At present, it remains unknown whether early-life factors are also associated with the development of MONW. Finding early predictors of MONW could help identifying individuals at high risk and developing appropriate interventions.

Here, we study associations between early-life factors and the MONW phenotype in 1 178 normal-weight participants of the Cardiovascular Risk in Young Finns study whose body weight and cardiometabolic risk factors were followed up from childhood to adulthood.

## Methods

*Study design and measurements*

The Cardiovascular Risk in Young Finns Study is an ongoing population-based follow-up study of atherosclerotic precursors (6). In 1980, a total of 4 320 Finnish children representing six different age cohorts (3, 6, 9, 12, 15, and 18 years of age) were invited, and 3 596 (83.2%) children participated in the first cross-sectional survey. In 2001 and 2011, a total of 2 620 participants aged 24-39 years, and 2 063 participants aged 34-49 years, respectively, were re-examined. The study was approved by the Ethics Committee of Hospital District of Southwest Finland in agreement with the Declaration of Helsinki, and all participants provided written informed consent. Adults with underweight (BMI<18.5 kg/m$^2$), overweight (BMI>25 kg/m$^2$), type 1 diabetes or pregnancy were excluded from the present analyses.

Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured from the brachial artery with a standard mercury sphygmomanometer in 1980 and with random zero sphygmomanometer in adulthood. The average of three measurements was used in the statistical analyses. Self-report questionnaires were used to obtain data on smoking, physical activity, birth weight, birth height, length of gestation, breastfeeding, and parental occupational status. Data on birth weight and height were verified by well-baby clinic records. Small for gestational age was defined as birth weight below the 10th percentile and large for gestational age as birth weight over the 90th percentile in the study population. Parental occupational status was divided into three categories: manual, lower-grade non-manual, and higher-grade non-manual. In 1980, 1983 and 1986, questionnaire information on cigarette smoking was collected in participants aged 12 years or older. Individuals who had reported daily smoking at any age between ages 12 and 18 were defined as smokers. Physical activity data were available for participants aged 9 years or older in 1980. A physical activity index was calculated as previously described (range 5–15) (7).

Venous blood samples were drawn after an overnight fast for determination of lipid, serum glucose and insulin concentrations. Serum insulin was measured with an immunoassay (8). Standard enzymatic methods were used for serum glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol (9, 10). Low-density lipoprotein cholesterol concentration was calculated by the Friedewald formula in subjects with triglycerides <4.0 mmol/L.

*Definition of the metabolically obese normal-weight phenotype*

MONW was defined as BMI 18.5-25 kg/m$^2$ in the presence of two or more components of the International Diabetes Federation (IDF) criteria for the metabolic syndrome (hypertriglyceridemia, low HDL cholesterol, high blood pressure, high fasting glucose) (11). The cut-off points for the risk factors were as follows: hypertriglyceridemia: ≥ 1.7 mmol/L; low HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or treatment for hypercholesterolemia; high blood pressure: systolic blood pressure ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension; high fasting glucose: ≥ 5.6 mmol/L, or previously diagnosed type 2 diabetes.

*Statistical analysis*

Values for insulin, triglycerides, HDL cholesterol, and LDL cholesterol were log-transformed before analyses because of skewed distributions. Logistic regression models were used to examine the associations between early-life factors and the risk of adult MONW. Continuous variables were z-score-transformed in the logistic regression analyses. Statistical analyses were performed with the IBM SPSS Statistics software, Version 21 (IBM Corp., Armonk, NY). The P value threshold for statistical significance was corrected for the number of early-life predictors tested using Bonferroni correction ($P_{BONFERRONI}$=0.05/17=0.0029).

## Results

*Early predictors of adult metabolically obese normal-weight phenotype*

Baseline characteristics of the study participants are shown in **Supplemental Table 1**. Of the 1 178 normal-weight adults (aged 24-39 years) included in the study, 141 (12.0 %) were defined as MONW in 2001. The strongest predictor of adult MONW in logistic regression models (adjusted for age, sex and BMI) was an increase in BMI z-score (zBMI) from childhood to adulthood (OR= 2.32 CI95% 1.79-3.01 per SD) (**Table 1**). Other significant predictors of the MONW phenotype were male sex (OR=2.04, CI95% 1.43-2.91), higher childhood concentration of LDL cholesterol (OR =1.43 CI95% 1.18-1.72 per SD) and triglycerides (OR= 1.40 CI 95% 1.17-1.67 per SD), and lower childhood concentration of HDL cholesterol (OR= 0.71 CI 95% 0.59-0.85 per SD).

To test which of the five identified early-life factors were independent predictors of the MONW phenotype, we included the five factors into a combined model, adjusting additionally for age and childhood BMI. All five predictors except triglycerides remained significant in the combined model ($p<0.0029$) (**Table 2**). Further adjustment for alcohol consumption, physical activity, or smoking in adulthood had no appreciable effect on the results (data not shown). Adjustment for adult waist circumference rendered the association of male sex with MONW non-significant (OR=1.20, CI 95%=0.67-2.16, p=0.54) while all other predictors remained statistically significant.

As a sensitivity analysis, we tested the predictive value of the five independent predictors for MONW after an additional ten years of follow-up in 2011, among 770 normal weight adults of whom 13.4% were MONW at the time. Of the early-life factors that were significantly associated with MONW in 2001 (**Table 2**), three predictors remained significant in 2011: an increase in zBMI from childhood to adulthood (OR=2.02, CI95% 1.43-2.68 per SD, $p=5.6x10^{-5}$), male sex (OR=3.21, CI 95%=2.03-5.07, $p=5.2x10^{-7}$), and lower childhood HDL cholesterol (OR=0.64, CI 95% 0.50-0.81 per SD, $p=2.2x10^{-4}$).

## Discussion

We found that an increase in BMI from childhood to adulthood was a strong predictor of adult MONW, suggesting that weight gain may be harmful to metabolic health even among normal-weight individuals. Other independent predictors of the adult MONW phenotype were male sex, higher childhood LDL cholesterol, and lower childhood HDL cholesterol.

The MONW phenotype is characterized by a poor capacity to expand subcutaneous adipose tissue, which may drive lipid accumulation and lipotoxic effects in visceral adipose tissue, liver, and skeletal muscle (12). Individuals with innately poor capacity for subcutaneous fat deposition may tend to retain normal weight from childhood to adulthood, but at the same time remain particularly vulnerable for exceeding their capacity for safe storage of fat when gaining weight, which may lead to premature development of cardiometabolic impairments (13). Alternatively, the adipose tissue of lean children may not adapt to positive energy balance during childhood to the same extent as that of children with overweight, which could make lean children particularly susceptible for developing adipose tissue dysfunction when gaining weight later in life (14).

Early in-utero programming may influence cardiometabolic risk parameters, including insulin sensitivity, ectopic lipid deposition and dyslipidaemia in adulthood (15). Recent findings suggest that being born small for gestational age may confer a higher risk of metabolically unhealthy obesity compared with being born with a birth weight appropriate for gestational age (16). We found that adults with MONW were more frequently born small for gestational age than adults with healthy normal weight. However, this association did not reach significance in logistic regression analyses. Further studies with larger sample sizes are needed to confirm or refute the link between being born small for gestational age and MONW in adulthood.

Consistent with previous findings in adults (4), we found that the risk of MONW was higher among men than in women. The higher risk was primarily explained by a higher waist circumference in men than in women, suggesting that men may be more vulnerable to metabolic impairments upon weight gain due to their increased tendency to accumulate abdominal fat (17). We also found that a higher concentration of LDL cholesterol and lower concentration of HDL cholesterol in childhood are independent predictors of

adult MONW. Our results are consistent with previous studies showing that lipid levels track from childhood to adulthood (18, 19).

**Conclusions**

Even in individuals who remain normal weight and particularly in men, relatively higher increase in adiposity from childhood to adulthood is harmful to cardiometabolic health, and early adoption of a healthy lifestyle is thus critical.

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A.V. researched data, A.V. and T.O.K wrote the manuscript. Other co-authors reviewed/edited the manuscript and contributed to data collection. A.V is the guarantor of the article and takes responsibility for the contents of the article.

Supplementary information is available at International Journal of Obesity's website.

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**Table 1. Age, sex and BMI-adjusted odds ratios of early-life factors for metabolically unhealthy normal weight in adulthood (n=1178)**

| Variable | OR | 95 % CI | P-value |
|---|---|---|---|
| **Change in zBMI from childhood to adulthood** | 2.32 | 1.79-3.01 | **$2.8x10^{-10}$** |
| **Male sex** | 2.04 | 1.43-2.91 | **$8.7x10^{-5}$** |
| **Small for gestational age[1]** | 1.78 | 0.99-3.18 | 0.053 |
| **Childhood LDL cholesterol** | 1.43 | 1.18-1.72 | **$2.1x10^{-4}$** |
| **Childhood triglycerides** | 1.40 | 1.17-1.67 | **$2.3x10^{-4}$** |
| **Childhood insulin** | 1.29 | 1.01-1.65 | 0.039 |
| **Childhood diastolic blood pressure** | 1.18 | 0.97-1.42 | 0.101 |
| **Childhood systolic blood pressure** | 1.15 | 0.93-1.42 | 0.204 |
| **Parental occupational status[2]** | 1.01 | 0.79-1.30 | 0.921 |
| **Mother's BMI[3]** | 0.99 | 0.82-1.20 | 0.921 |
| **Fathers' BMI[4]** | 0.97 | 0.80-1.19 | 0.782 |
| **Daily smoking in the age 12-18 years[5]** | 0.92 | 0.57-1.49 | 0.729 |
| **Childhood physical activity index[6]** | 0.84 | 0.68-1.04 | 0.101 |
| **Childhood zBMI** | 0.79 | 0.65-0.95 | 0.014 |
| **Childhood HDL cholesterol** | 0.71 | 0.59-0.85 | **$1.7x10^{-4}$** |
| **Large for gestational age[1]** | 0.69 | 0.27-1.77 | 0.439 |

Continuous variables were standardized. OR, odds ratio; CI, confidence interval; z-BMI, age and sex adjusted z-score for body mass index. Adjusted p-values <0.0029 were considered statistically significant.

[1]n=914

[2]Three categories according to a parental occupation (manual, lower-grade nonmanual, higher-grade nonmanual) (n=1168), [3]1133, [4]1029,[5] In 1980, 1983 and 1986, questionnaire information on cigarette smoking was collected in participants aged 12 years or older (n=1095), [6]n=757.

| Table 2. Multivariable odds ratios of childhood risk factors for MONW in adulthood (2001) | | | |
|---|---|---|---|
| **Variable** | **OR** | **95 % CI** | **P-value** |
| **Change in zBMI from childhood to adulthood** | 2.56 | 1.94-3.38 | **$3.1x10^{-11}$** |
| **Male sex** | 2.38 | 1.63-3.47 | **$7.0x10^{-6}$** |
| **Childhood LDL cholesterol** | 1.41 | 1.14-1.73 | **0.001** |
| **Childhood zBMI** | 1.26 | 0.97-1.63 | 0.082 |
| **Childhood triglycerides** | 1.18 | 0.97-1.45 | 0.100 |
| **Age** | 1.02 | 0.98-1.06 | 0.314 |
| **Childhood HDL cholesterol** | 0.66 | 0.54-0.81 | **$5.4x10^{-5}$** |

Continuous variables were standardized. Age-, sex- and BMI-adjusted significant variables were selected in the model. OR, odds ratio; CI, confidence interval; z-BMI, age and sex-adjusted body mass index z-score. Adjusted p-values <0.0029 are considered statistically significant.