Growth, body composition, and cardiovascular and nutritional risk of 5-10-year-old children consuming vegetarian, vegan or omnivore diets.

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Short title: Health outcomes of plant-based diets in children

Abbreviation list:

25(OH)D - 25-hydroxy vitamin D

BA - bone area

BMAD - bone mineral apparent density

BMC - bone mineral content

CC - complete case

cIMT- carotid intima-media thickness

CPM - counts per minute

CVD - cardiovascular

DAG - directed acyclic graph

FMI - fat mass index

Hb - hemoglobin

HTC - hematocrit

Hs-CRP - high-sensitivity C-reactive protein

IFGBP3 - insulin growth factor binding protein 3

IGF1 - insulin-like growth factor 1

LMI - lean mass index

MCV - mean corpuscular volume

MI - multiple imputation

MVPA - moderate and vigorous physical activity

NCD - non-communicable disease

PA - physical activity

PBD - plant based diets

RBC - red blood cells

SES – socioeconomic status

TBLH BMC - total body less head bone mineral content

TBW - total body water

ABSTRACT

Background: Plant-based diets (PBD) are increasingly recommended for human and planetary health. However, comprehensive evidence on the health effects of PBD in children remains incomplete, particularly in vegans.

Objectives: To quantify differences in body composition, cardiovascular risk and micronutrient status of vegetarian and vegan children relative to omnivores, and to estimate prevalences of abnormal micronutrient and cholesterol status in each group.

Methods: In a cross-sectional study, Polish children aged 5-10 years (63 vegetarian, 52 vegan, 72 matched omnivores) were assessed using anthropometry, deuterium dilution, DXA and carotid ultrasound. Fasting blood samples, dietary intake and accelerometry data were collected.

Results: Results are reported relative to omnivores. Vegetarians had lower gluteo-femoral adiposity, but similar total fat and lean mass. Vegans had lower fat indices in all regions but similar lean mass. Both groups had lower bone mineral content (BMC). The difference for vegetarians attenuated after accounting for body size, however in vegans remained (total-body less head -3.7%;95% CI:-7.0,-0.4; lumbar spine -5.6%;-10.6,-0.5;). Vegetarians had lower total cholesterol, high-density lipoprotein (HDL), and lower serum B12 and 25-hydroxyvitamin D (25(OH)D) without supplementation, but higher glucose, very low-density lipoprotein, and triglycerides. Vegans were shorter, had lower total, low-density lipoprotein (LDL) (-24mg/dL;-35.2,-12.9) and HDL (-12.2 mg/dL;-17.3,-7.1), high-sensitivity C-reactive protein, iron status, and lower serum B12 (-217.6 pmol/L;-305.7, -129.5) and 25(OH)D without supplementation, but higher homocysteine and mean corpuscular volume. Vitamin B12 deficiency, iron-deficiency anemia, low ferritin and low HDL were more prevalent

in vegans, who also had the lowest prevalence of high LDL. Supplementation resolved low B12 and 25(OH)D levels.

Conclusions: Vegan diets were associated with healthier cardiovascular risk profile, but also with increased risk of nutritional deficiencies, and lower BMC and height. Vegetarians showed less pronounced nutritional deficiencies, but unexpectedly, less favourable cardiometabolic risk profile. Further research may help maximise the benefits of PBD in children.

Keywords: stature, bone mineral content, iron deficiency, vitamin B12 deficiency, vitamin D deficiency, cardiovascular risk, vegetarian children, vegan children.

INTRODUCTION

Recently, interest in plant-based diets (PBD) has increased in many global regions. Though formal estimates are lacking, numerous sources indicate that more people are adopting meat-free diets in industrialised countries (1,2). Broadly, vegetarian diets exclude meat and fish, while vegan diets eliminate all products of animal origin, including dairy and eggs (3). There are three main reasons for their rising popularity: planetary sustainability, improving health including prevention of non-communicable disease (NCD), and heightened concern for animal welfare (4,5). The first two have been recently reflected in healthy eating recommendations by numerous international health organisations (5,6). These issues primarily concern adults, who may then act on them when selecting diets for their offspring. The health effects of vegetarianism and veganism have been evaluated in adults and include lower cardiometabolic risk (7), but increased fracture risk in vegans with low dietary calcium content (8).

Less evidence is available for children. Atherosclerosis originates in childhood, and relates to cardiometabolic risk factors that, along with dietary habits, track into adulthood. Therefore PBD in childhood might reduce adult risk of cardiovascular disease (CVD) (9); however any such benefits must be considered in light of safety in the pediatric population. Vegetarians and vegans restrict intake of whole food groups. This is of particular concern in children, whose nutrient and energy needs are higher relative to body weight and whose growth might be impaired by nutrient deficiencies at sensitive periods of development (10). Existing data come from studies of heterogenous design, and relate predominantly to anthropometric outcomes, and to vegetarian children. Previous work on vegetarian children showed normal growth and a tendency to be leaner compared to omnivores (11). Evidence on blood micronutrient status for this group is available primarily for iron status, showing wide

variation in the prevalence of deficiency (12). Data on other blood parameters is scant (11,13). There are no current informative studies on vegan children other than those <3 years old (14) when health effects might be less evident.

The sparsity of evidence contributes to inconsistencies between medical and nutrition organisations' statements regarding the safety of meat-free diets in childhood (15–19). Given growing global campaigns to encourage PBD, reliable evidence is urgently needed, so that these diets can help decrease ecological damage while also promoting health in both adults and children. We aimed to evaluate differences in several indicators of health, including growth, body composition, CVD risk and micronutrient status, along with estimating the prevalence of inadequate serum micronutrient and abnormal cholesterol status in vegetarian or vegan children, relative to an omnivore reference group.

METHODS

Study design

A cross-sectional methodology was chosen for this study. Although intervention trials are ideal for providing evidence for a causal relationship, it is unethical and unfeasible to randomise healthy children to different dietary regimens of unknown health effects for periods long enough to elicit effects on growth, body composition or selected CVD risk factors. Although our study is cross-sectional, the exposure tracks back into the past, i.e. the children recruited to the study had to have followed their respective diets for at least one year and their diet was measured within two weeks before the outcome data collection took place.

Subjects

We studied healthy Polish children (age 5-10 years), all of white European ethnicity. All children had to have followed their diet for ≥1 year prior to participation. Exclusion criteria included receiving any treatment other than bronchodilators and/or steroids for asthma; or conditions adversely affecting growth and development. The latter included obesity and wasting defined using age-specific pediatric international BMI cut-offs, corresponding to 30 kg/m^2 at age 18 years and -2 z-scores respectively (20,21), as these suggest malnutrition regardless of dietary choice; and height <5th percentile for Polish growth curves (22) due to a diagnosed growth disorder. Eligibility was established via electronic questionnaires sent to parents before the study and confirmed during data collection.

Recruitment and sampling

Vegan and vegetarian children were recruited by advertisements using internet portals and social media, targeting issues of vegetarianism and veganism. Omnivores were recruited by asking vegan and vegetarian children to bring a friend of the same sex and similar age (within +/- 1-year difference). Additionally, advertisements were placed in health-food stores, and on internet portals devoted to healthy eating, from which omnivores were matched to vegetarians and vegans by sex, age (+/- 1 year), maternal education (higher, secondary, primary), and place of residence (urban vs. rural).

The sample size per group was calculated using data for blood lipids (total and low-density lipoprotein cholesterol (LDL-C)) from a pilot study, investigating blood lipid levels in healthy Polish prepubertal children on vegan (n=46) or vegetarian (n=29) diets in comparison with age- and sex-matched omnivores (n=61) in 2010. We aimed

to detect, with 80% power and a significance level alpha of 0.05, mean differences ≥0.5 z-score between omnivore and either vegan or vegetarian groups in each outcome, requiring 64 children per group. Anticipating occasional missing data, we intended to recruit 66 children per group. We specified age groups for recruitment taking into account both the scarcity of vegan children in Poland, and the aim of achieving similar age distributions across dietary groups. We aimed to recruit 7 of each sex-diet combination at 5 years, and 13 in the 6-7 and 8-10-year age-groups (total 198). Recruitment lasted from June 2014 until July 2016.

Background characteristics

The following family data were collected before enrolment via an electronic questionnaire: child's date of birth, parent-reported weight and height, current health status, medications, information on parental smoking and educational attainment, crude information on income level per person in the household, family size, family history of NCD, (parental/grandparental hypertension, obesity, diabetes or coronary artery disease or myocardial infarction before age 55 years for men and 65 for women), religion, breastfeeding/formula feeding practices, and the present and past frequency of animal product consumption. During recruitment, additional questionnaires in the clinic ascertained the child's birth order, fracture history, lactose intolerance status, birth weight, APGAR score, gestational age, self-reported parental height, maternal pre-pregnancy nutritional status (weight, nutritional supplementation practices, dietary practices), and if the child had been on holiday with significant sun exposure recently.

Physical activity

Physical activity (PA) was measured by Actigraph GT1M accelerometers. Children were asked to wear an accelerometer on the right hip during waking hours for 4 days. A minimum of 2 days with ≥8 hours of activity recordings was deemed valid (23,24). We used average counts per minute (CPM) as an indicator of overall activity. Additionally, time spent in sedentary, moderate and vigorous PA was extracted to compare time spent at different PA intensity levels between dietary groups.

Exposure - dietary assessment and categorisation

Prior to recruitment, parents completed a screener questionnaire to quantify the child's frequency of consumption of meat, fish, dairy products and eggs in the last 12 months. The screener questionnaire was used to recruit and classify children as omnivore, vegetarian or vegan, and to assess the frequency of animal product consumption from birth.

Food diaries were used to assess dietary intake. Parents/guardians recorded everything eaten or drunk over four consecutive days, including two weekend days. The records were obtained within the two weeks before physiological data collection, as most of the blood biochemicals of interest respond to dietary changes within that time (25–27). Thorough written instructions, along with pictures of household measures of food and drinks, were provided. Two telephone calls were made to explain the written instructions, to answer questions and to check compliance. Involvement of school or kindergarten staff in keeping the record prospectively was encouraged. If insufficient details were obtained by parents on the composition of meals eaten outside of the home, schools, kindergartens, or restaurants were directly contacted by the research team. The staff provided recipes of meals cooked or

158 served and information on the quantity of foods consumed by children at their eating
159 establishment.

160 Estimated food intakes were entered into nutritional analysis software (Esha Food
161 Processor, version 10.14), by two dieticians. Polish food composition tables (28)
162 linked to the software were used as the primary reference for calculating nutrient
163 intakes. Nutrient content of foods not available in the Polish tables, e.g. vegetarian-
164 specific foods, was obtained from the database of the US Department of Agriculture
165 (29). Final classification into dietary groups was performed after analysing the food
166 diaries. Participants were classified as vegan if they consumed no flesh foods (meat
167 and fish) or other animal-based products (eggs, dairy) for at least the previous year,
168 or if they consumed no flesh foods (meat and fish) and nearly no other animal-based
169 products (eggs, dairy) over the last year, with minor exceptions that amounted to
170 <5% of dietary energy from eggs and dairy estimated from the food diary. The
171 dieticians responsible for diary data entry were blinded to this cut-off value.
172 Vegetarians were classified as those consuming eggs and dairy ≥1 per month, but
173 red meat, poultry and fish <1 per month, for at least the previous year. For clear
174 distinction of dietary patterns, the study did not accept pesco-vegetarians (those who
175 consume red meat and poultry <1 per month, and fish ≥1 per month), and semi-
176 vegetarians (who consume red meat, poultry, fish 1 per month to 1 per week, and
177 eggs or dairy at any level), and defined as omnivores those who eat meat, poultry,
178 fish >1 per week, and eggs or dairy at any level (30). For the purpose of this paper,
179 selected dietary data will be presented as background characteristics only, in order to
180 help interpret health outcome differences. More detailed dietary analysis will follow in
181 a separate publication. Definitions of terms describing different types of plant -based
182 diets used in this paper are presented in supplementary table 1.

Outcomes

Our outcomes were anthropometry, body composition, bone health, CVD risk markers and micronutrient status (iron, B12 and 25-hydroxy vitamin D ((25 (OH) D)). These were measured after dietary data was collected during the child's one-day visit to the clinic, from September 2014 until July 2017.

Anthropometry and body composition

Weight and height; mid-thigh, waist and hip girths; biceps, triceps, subscapular and suprailiac skinfolds, were all measured by two trained raters according to the standard operating procedures of University College London (UCL) Institute of Child Health. The digital scales (Seca 86l) were regularly calibrated. Height was measured with a portable stadiometer to the nearest 0.5 cm (Seca 213), skinfolds with callipers (Harpenden) and girths with a non-stretchable tape. Body composition was assessed using deuterium (D_2O) dilution to measure total body water (TBW, litres), using an oral dose equivalent to 0.05 g/kg body weight. Saliva samples were collected using cotton wool swabs at baseline, and 4 h after dosing. Isotopic enrichment of saliva samples and the dose administered was determined by isotope-ratio mass-spectrometry (Gasbench-Delta XP system, ThermoFisher). Lean mass (used synonymously here with fat-free mass) was calculated from TBW using published hydration coefficients (31), and fat mass calculated as difference of body mass and lean mass. We normalized body composition for height by dividing by height-squared, giving the lean mass index (LMI), and fat mass index (FMI) in the same kg/m^2 units as BMI. Body composition z-scores were derived from UK reference data (31).

Total body bone mineral content (BMC) and lumbar spine BMC were assessed by Dual-energy X-ray absorptiometry (Lunar Prodigy Advance). For the calibration of the densitometer, a daily quality control procedure was performed. Additionally, an anthropometric spine phantom was scanned at least twice weekly. The technician was blind to participants' dietary exposure. The subject wore light indoor clothing. We extracted BMC for the total body minus the head (TBLH BMC), and the L2-L4 region (L2-L4 BMC), along with the corresponding bone areas (BA) in order to correct results for bone size. For this purpose we also calculated bone mineral apparent density (BMAD) using the Carter method, which adjusts BMC for calculated bone volume rather than bone area (32), utilizing data for age, sex, BMC, and bone area for L2-L4. We used UK reference data (33) to obtain BMAD z-scores.

Cardiovascular risk and micronutrient status

Fasting blood (15 ml) was drawn between 8 and 10 am. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C, very low-density lipoprotein cholesterol (VLDL-C), and triglycerides were analysed by agarose gel electrophoresis (A15 Biochemistry Analyser, Biosystems). The complete blood count was determined by the impedance method (Coulter LH 750). Fasting glucose was analysed by an enzymatic spectrophotometric method (A15 Biochemistry Analyser). Plasma vitamin B12 and homocysteine were determined by Chemiluminescent Microparticle Immunoassay (CMIA) using commercial kits (Architech i1000SR Analyzer, Abbott). Insulin was determined by Immunoradiometric Assay (IRMA) (KIP1251 kit, DiaSource). IGF-1 was determined by Radioimmunoassay (RIA) (KIP1589 kit, DiaSource), using the Automatic Gamma counter 1470 Wizard (Perkin Elmer). IGFBP-3 was determined by sandwich ELISA method (E03A kit, BioVendor)

on an ELISA Plate Reader (PowerWave XS Bio-TEK). The IGF-1/IGFBP-3 molar ratio was calculated according to the formula: 1 ng/mL IGF-1 = 0.130 nmol IGF-1 and 1 ng/mL IGFBP-3 = 0.036 nmol IGFBP-3 (34). 25(OH)D was measured by chemiluminescent immunoassay (CLIA) (IDS iSYS Analyser). Ferritin was ascertained by immunochemiluminescence, and high-sensitivity C-reactive protein (hs-CRP) by immunoturbidimetry (Cobas 600). Hs-CRP and ferritin were analysed from frozen 3 ml samples remaining 3 years after the original data collection started. Homeostasis model assessment (HOMA-IR) was used to assess insulin resistance, calculated as fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5 (35). Nurses, laboratory staff were blinded to dietary exposure. Systolic and diastolic blood pressure were measured using an electronic blood pressure monitor (OMRON 7080) after 10 minutes rest, with the child seated and quiet.

Carotid intima-media thickness (cIMT) was evaluated by ultrasonography. All measurements were performed by the same examiner blinded to dietary exposure using an Hitachi Aloka Prosound Alpha 6 and a 5.5 to 12.5-MHz probe. CIMT was measured bilaterally on the common carotid arteries according to methodology described previously (36).

Ethics: The study was approved by Ethical Committees of UCL and the Children's Memorial Health Institute in Warsaw, Poland, where the study took place. Parents gave written informed consent, and children assented to participate. All participants were offered a nutritional consultation by a clinical dietician on the day data collection took place. Parents were contacted immediately and given additional nutritional or medical advice if abnormal results were found.

Statistical analyses

To describe the background characteristics of the diet groups, means and SDs or medians and inter-quartile ranges (IQR) were calculated. All dietary background characteristics were expressed as medians, as distributions of nutrient intakes have a right-skewedness. To test the null hypothesis of no difference between the groups, chi-square, ANOVA or Kruskall-Wallis tests, were applied

For anthropometric outcomes ascertained by two raters, we confirmed inter-rater reliability by computing interclass correlation coefficients and t-tests of differences between raters' means. To compare means in the main outcomes across diet groups we used linear regression models, with vegetarians or vegans compared to the reference group of omnivores. Cluster–robust standard errors were used to calculate 95% confidence intervals (CIs) to account for clustering of siblings (37). We natural log-transformed outcomes that were not symmetrically distributed (HOMA-IR, VLDL-C, triglycerides, hs-CRP, TBLH-BMC, L2-L4 BMC, ferritin and homocysteine), with differences between groups in these outcomes expressed on a percentage scale (38). This approach was selected because models fitted on the log scale improve the numerical quality of the estimation procedure, whereas confidence intervals for models fitted on the original scale would be large and asymmetric, and hence difficult to interpret. However, all estimates and their CI's in the original scale are given in the supplementary material.

We excluded two physiologically implausible values (insulin: 29.2 µUI/mL; hs-CRP: 15.79 mg/dL), and divided in two the lowest detectable concentration levels of two variables, vitamin B12 and 25(OH) D that had values < 69 pmol/L and <17.5 nmol/L respectively, to address truncation due to limits of detection of the instrument. The

blood pressure monitor failed in those with arm girth <17cm and >22cm (n=39), all blood pressure data were therefore excluded from analysis.

Directed acyclic graphs (DAGs) were used to state our assumptions about the inter-relationships of numerous variables, including background characteristics of dietary groups, associated with the exposure and each set of outcomes and exposure correlates (namely, anthropometry and body composition; bone; CVD risk; iron and vitamin B12; 25 (OH) D and nutritional intake). This helped us identify a minimum set of confounders to control for (39) according to the most recent theoretical and methodological developments in casual inference (40).

Linear regression models were then fitted for each set of outcomes on diet group that controlled for the relevant (often different) potential confounders. The simplest models included diet group (the exposure) and – if relevant for the outcome – age and sex (models 1). These are presented to aid elucidation of the effect of confounding present in the data. A more complex model (models 2) included further confounders identified by the relevant DAG. Additional models were fitted for some outcomes where mediators (i.e. variables assumed to be on the causal pathway from exposure to outcome) were also controlled for to examine possible pathways of association, assuming that no additional confounders may be at play (models 3). Confounders which had biologically plausible non-linear relationships with the outcome (birth weight, gestational age, maternal pre-pregnancy BMI) were categorised into fifths and used in the analysis as categorical variables. In the analyses of serum parameters of vitamin B12 and 25 (OH) D, dietary groups were further separated into whether or not the child was given vitamin supplements or vitamin-fortified foods. Seasonality in concentrations of vitamin 25 (OH) D was

adjusted for by including sine and cosine functions of the day of the year of the blood draw in models with this outcome (41,42).

Multiple imputation using chained equations (43) was applied to deal with missing values that affected some explanatory variables (birth weight, gestational age, maternal pre-pregnancy BMI, average CPM, paternal education and height, religion, FMI, LMI), under the assumption of missing at random (44).

Separate to the above, in secondary analyses ordinal logistic regression analysis was used to compute marginal predictions of the prevalence of several categories of inadequate status of vitamin B12, iron and cholesterol in the three diet groups. Pairwise comparisons of the marginal predictions were used. The ordinal logistic models included the indicators of diet group, and confounders identified by the respective DAGs for the corresponding continuous outcomes. Probable and possible vitamin B12 deficiency were defined as <148pmol/L and 148 to 258pg/ pmol/L, respectively (45). Iron deficiency anemia was defined, following WHO (46), as mild (hemoglobin (Hb) 11.0–11.4 g/dL), moderate (Hb 8.00–10.9 g/dL) or severe (Hb <8 g/dL). Cut-offs for abnormally low serum ferritin levels were defined as <15 µg/l, following WHO (47), that identified it as depleted iron stores. Pediatric LDL-C values were classified, following the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (48), as high (≥130 mg/dL), borderline (110–129 mg/dL) or acceptable (<110 mg/dL); and HDL-C as low (<40 mg/dL), borderline (40–45 mg/dL) or acceptable (>45 mg/dL). The results of complete case (CC) and multiple imputation (MI) analyses were compared. All statistical analyses were performed in Stata release 13.1 (Stata-Corp, College Station, Texas, USA). A two-sided p-value of 0.05 was used as the threshold for statistical significance.

This is investigation has an exploratory nature, as some of the health parameters have not been investigated previously in this group, especially in vegans. Hence, corrections for multiple testing were not carried out. Another reason is that this study aimed to assess the safety of PBD in children, which is more important than detecting differences in their potential CVD benefits, and correction for multiple testing could have obscured evidence suggesting adverse effects. However, the percentage of false positive results is likely to be lower than that expected from the number of tests in this study, as several health outcomes were tested with more than one method, and in those cases, are affected by a single biological relationship.

RESULTS

Background characteristics

We assessed 256 children for eligibility and excluded 64 omnivores who did not meet the matching criteria. We thus recruited 192 children, of which 74 were omnivores (36 boys), 64 vegetarians (31 boys) and 54 vegans (24 boys) (**Figure 1**). Five were disqualified for not fulfilling inclusion criteria. The reasons included suspected coeliac disease and recent active weight loss (2 omnivore boys), consuming fish > once a month (1 girl from the vegetarian group), and suspected growth disorder due to abnormal IGF-1 and growth hormone concentrations (2 vegan boys). This left 187 children in the analysis, 72 omnivores (34 boys), 63 vegetarians (31 boys) and 52 vegans (22 boys). **Table 1** summarizes background characteristics by diet group.

There were no meaningful differences in age or sex between groups. Overall, most children from all dietary groups lived in cities or towns, came mainly from high-educated families, although there was a trend among the mothers of vegans and vegetarians to be less educated. Vegans were more likely than the other groups to

have never been formula-fed, and to have non-smoking parents. However, all families from this study compared favourably to the general Polish population in terms of smoking prevalence and breastfeeding duration (49–51). Vegans and vegetarians were more likely than omnivores to have a family history of coronary heart disease, and to have atheist parents. The groups did not differ with regards to the remaining perinatal characteristics and socioeconomic status (SES) or PA, both in terms of average movement count and PA intensity.

Supplementation and fortification practices are presented in **table 1.** Nearly a third of children on either vegetarian or vegan diets were not given any B12 supplements or B12 fortified foods, and around the same proportion used vitamin D supplements. Dietary background characteristics are presented in supplementary table 1. The diet groups varied in their intake of most nutrients. Omnivores had the highest and vegans the lowest estimated intakes of protein, sucrose, total, saturated and monounsaturated fat, cholesterol, vitamin B12 and vitamin D. Vegans had the highest and omnivores had the lowest estimated intake of total carbohydrates, starch, dietary fiber, polyunsaturated fat, folate, carotenoids, vitamin C, magnesium, and iron. Vegetarians had the highest estimated intake of calcium, while vegans markedly the lowest. There were no meaningful differences in estimated energy intake. The mean duration of exposure to meatless diets was 5.3 (SD ±2.4) years for vegans and 5.9 (SD ±2.0) years for vegetarians. Although the inclusion criteria stated that the children recruited to the study had to have followed their respective diets for at least one year, in actuality 85% of the vegetarians and vegans had followed their diets for 3 years or more, while the remaining 15% had followed their diets for at least 2 years.

Health outcomes

Minimally adjusted results (models 1) are presented in the tables to appreciate the extent of confounding present in the data. Unless otherwise specified below, only the multivariable-adjusted, multiple-imputed results for mean differences in outcomes between vegetarians or vegans compared to the reference group of omnivores (models 2, 3) are described in the results section, as they are meant to represent the causal effects of interest. Complete case analyses (**supplementary tables 3-8**) and crude means of all outcomes (**supplementary table 9**) are included in the supplementary material.

Anthropometry and body composition

Mean differences with 95% CI for anthropometric and body composition outcomes of vegetarians and vegans relative to omnivores are presented in **table 2.** On average, both vegetarians and vegans were shorter than omnivores (Δ-0.32 and -0.57 height z-score respectively) which corresponded to Δ-1.9 and -3.15 cm, although the difference in vegetarians was non - significant. In comparison to omnivores, both vegetarians and vegans had lower thigh z-scores, whereas vegans but not vegetarians had lower BMI, FMI, suprailiac and triceps skinfold along with hip z-scores. However, there was no evidence of differences in LMI, biceps and subscapular skinfold or waist circumference, between dietary groups.

Bone health, cardiovascular risk and body iron status

Mean differences in bone, cardiovascular and body iron status outcomes are presented in **table 3**. Vegetarians and vegans had 7.3% and 15.2% respectively lower TBLH BMC than omnivores. These differences attenuated to the null in vegetarians and were attenuated in vegans to Δ - 3.7% after adjusting for presumed

mediators (height and weight z-scores, bone area) (model 3). Therefore, the deficit in bone mass in vegetarians and vegans was mostly explained by the effect of diet on body and bone size, however, not entirely in vegans. For L2-L4 BMC the deficits relative to omnivores were detected in vegans only (Δ-9.3%). They were attenuated to Δ-5.6% after adjusting for the presumed mediators (model 3). These results were confirmed by another approach (BMAD) correcting for bone size, whereby both BMAD z- score and percentile were significantly lower for vegans only.

Table 3 also shows that diet was associated with differences in several CVD risk factors. Overall, vegans had on average lower total cholesterol, HDL-C, LDL-C, and hs-CRP than omnivores. Further adjustment for presumed mediators (height, fat and lean mass; model 3) only slightly attenuated the magnitude of the differences, except for HDL-C where the difference increased. The differences in hs-CRP remained after excluding 3 outlier values (>1mg/dL).

Vegetarians, in contrast, had lower average total cholesterol and HDL-C, however the magnitude of the difference in relation to omnivores was smaller than that of the vegans. They also had higher average fasting glucose, VLDL-C, and triglycerides. Model 3 shows strengthened differences between omnivores and vegetarians in glucose, HDL-C, VLDL-C, and triglycerides. In this model, the difference in total cholesterol in vegetarians attenuated to the null and HOMA-IR became significantly higher. There was no evidence of differences in insulin levels, a surrogate marker of atherosclerosis (cIMT), IGFBP-3, IGF-1 concentrations or molar ratio of IGF1:IGFBP3 levels or across the three diet groups.

Mean differences between diet groups in selected serum indicators of iron status are presented in the last part of **table 3**. Vegans had lower concentrations of mean red

blood cells (RBC), hemoglobin, hematocrit (HTC) and ferritin. Vegetarians did not differ in any of the iron status indicators from the omnivores.

Serum indicators of vitamin B12 and vitamin D status

Differences between diet groups in selected serum indicators of B12 status (serum B12, homocysteine, mean corpuscular volume (MCV)), addressing variation in supplementation and fortification practices, are presented in **table 4**. Vegans had lower mean serum B12 concentrations than omnivores if they were not given vitamin B12 supplements or B12 fortified foods (Δ-217.6 pmol/L), or if they were given B12 fortified foods without B12 supplementation (Δ-139.8 pmol/L). Additionally, vegans who were not given B12 supplements or B12 fortified foods had higher mean homocysteine and MCV concentrations than omnivores. Vegetarians had lower serum vitamin B12 (Δ-90.9 pmol/L) and higher homocysteine than omnivores, if they were not given vitamin B12 supplements or B12 fortified foods. There were no differences in serum vitamin B12, mean homocysteine or MCV concentrations in vegetarians who were given foods fortified with B12, and vegetarians and vegans who were given B12 supplements and B12 fortified foods, in comparison to omnivores. Mean differences between groups in serum 25(OH)D are presented in **table 5**. Vegetarians and vegans who did not use supplements had lower 25(OH)D concentrations (Δ-7.1 and Δ-13.3 nmol/L, respectively) than omnivores. Supplementing vegetarians had higher concentrations than omnivores.

Prevalence of abnormal vitamin B12, HGB, depleted iron stores and LDL- and HDL-cholesterol status

Estimated prevalences and pairwise comparisons of abnormal vitamin B12, HGB, depleted iron stores, LDL- and HDL-cholesterol status in dietary groups are presented in **table 6**. For most of these comparisons, the estimated prevalences significantly differed between the vegans and the omnivores. The prevalence of probable vitamin B12 deficiency was 3% in omnivores, 4% among vegetarians and 13% in vegans. The prevalence of possible B12 deficiency was 16%, 19% and 40% in omnivores, vegetarians and vegans respectively. The prevalence of moderate iron deficiency anemia was 0% among omnivores, 2% in both vegetarians and vegans. The prevalence of mild anemia was 0% in omnivores, 7% in vegetarians, and 6% in vegans. There were no children with severe iron deficiency anemia. The prevalence of depleted iron stores (serum ferritin <15 µg/l), was 12.8% in omnivores, 18.3% in vegetarians and 30.2 % in vegans. The prevalence of abnormal pediatric LDL cholesterol status with high (≥130mg/dl) and borderline high (110–129 mg/dl) LDL-C concentrations was 13% and 17% for omnivores; 6% and 10% for vegetarians and 0% and 1% for vegans. The prevalence of low (>45 mg/dL) and borderline (40–45 mg/dL) HDL-C was 7% and 12% for omnivores, 15% and 19% for vegetarians and 26% and 24% for vegans.

There were no meaningful differences between the CC and MI analyses.

DISCUSSION

We recruited 3 groups of children consuming varying amounts of animal-source foods, reflected in contrasting macro- and micro-nutrient intakes. We found differences in several outcomes in vegetarians and vegans relative to omnivores. Vegan children had more favorable values for several cardiometabolic risk factors and lower fat mass, but also decreased stature, BMC and lower blood micronutrient status. Vegetarians unexpectedly showed a less favourable cardiometabolic risk factor profile; however other differences were less pronounced. Cardiometabolic risk differences persisted after adjusting for body composition, increasing confidence in our hypothesis that diet itself plays a causal role. Our data indicate that low serum B12 and 25(OH) D could be rectified by supplementation.

Most previous studies of PBD in children had limited sample size and heterogenous dietary classification criteria, examined few health parameters, and lacked adequate controls (11). Studies of vegan children addressed mainly anthropometry and/or lacked a reference group (52–54). Our results are broadly consistent with previous research, but provide more comprehensive data. Most other studies showed anthropometric measures of children following meatless diets were similar to or below the reference group. It was hypothesized that differences in PA might have contributed to lower fat mass, but we found no such difference. This suggests diet itself is the causal factor (11), given lack of differences in energy intake.

It is well established that B12 deficiency is an avoidable risk of vegan diets *per se*, and that vegans may also be in particular need of vitamin D supplementation when sunlight exposure is limited. However, evidence comes primarily from adults (55,56), and our study adds new data for both vegan and vegetarian children, demonstrating inadequate B12 status in unsupplemented diets, better levels in fortified diets, and in

vegans, optimal levels when diets incorporate fortification and supplements. Likewise, we show significantly lower values of vitamin D in vegetarians and vegans relative to omnivores, that are resolved in those in who take supplements. We also provide new data showing lower BMC in vegan children but no difference in vegetarians compared to omnivores, adjusting for body size. Finally, we generated novel data showing lower cholesterol and hs-CRP concentrations in vegans, but no differences in IGF-1, IGFBP3 or cIMT in either PBD group compared to omnivores. Although many of the coefficients for between-group differences are of modest magnitude, upward or downward shifts in population distributions affect how many individuals are in high or low risk groups. Among adults, vegetarians and vegans tend to have better cardiometabolic profile than omnivores and ~25% lower risk of ischemic heart disease (9). Importantly, atherosclerosis starts in childhood, and develops into classical CVD risk factors, which track through to adulthood. These risk factors are affected by diet (9), which itself tracks into adulthood (9). Our finding that vegan diets in children are associated with a better CVD profile might potentially contribute to lowering adulthood CVD. However, we also show that poorly planned PBD might worsen CVD profile already in childhood, and in adults such diets are linked to adverse CVD outcomes (57).

Beyond CVD risk, our study addresses knowledge gaps regarding the safety of PBD in children. Our data suggest that restriction of animal-based foods could prevent children from achieving optimal height or bone mineral status, and could lead to selected nutritional deficiencies. The shorter height of children consuming PBD may have mixed implications for long-term health. Taller height is associated with higher social status, and this association may be causal rather than just an artefact of social correlates (58,59).Taller adult height is associated with lower risk of NCDs (eg

diabetes, heart disease), though also with greater risk of diverse cancers (60). However, whether these height differences will persist into adulthood is unclear.

The findings for BMC are concerning. Maximising pediatric BMC is recommended (61) to promote peak BMC with the aim of reducing osteoporosis and fracture risk in adulthood. We found that vegans have lower BMC even after accounting for smaller body and bone size. It does not seem optimal to enter adolescence, a phase when bone-specific nutrient needs are higher, with a BMC deficit already established. If such deficits are caused by a diet that persists into adolescence, this might increase the risk of adverse bone outcomes later in life.

The main strength of our study is the detailed assessment of diet and health, to identify both risks and benefits of specific PBDs. We recruited adequate numbers to detect ≥0.55 SD difference in outcomes. The diet groups were matched for age, sex, and SES. We addressed a range of known potential confounders, measuring PA objectively and body composition via 3 independent techniques. Our results are corroborated by the children's nutrient profiles. In vegans, high estimated intakes of fiber, folate, vitamin C, carotenoids and magnesium, and low saturated fat, cholesterol and sucrose, indicate an 'unprocessed' type of PBD, which may explain their more favourable CVD risk profile. Conversely, their lower protein, calcium, B12 and vitamin D intakes may explain their less favourable BMC and serum vitamin levels. We speculate that protein quality in vegans might have contributed to the BMC findings (61), but further work is merited. The vegetarians' nutrient intake suggests a more processed type of PBD, which might explain their worse CVD risk profile. Consistent with adult studies (62), higher intakes of non-haem iron (the less bioavailable form) in vegetarians and vegans were accompanied by lower iron status.

The main limitation of our study was its cross-sectional design. We used convenience sampling of vegans and vegetarians as the only feasible method in this hard-to-reach population. Thus, this study was at risk of selection bias, which should be considered as a potential alternative explanation for some of the findings. Other limitations include small levels of missing data and faulty operation of the blood pressure monitor, obliging us to discard this data. Additionally, homocysteine is less specific than methylmalonic acid as a second-line test in assessing cobalamin disorders(45). However, it is widely used in similar studies, and was chosen to increase comparability of our data. Finally, our findings might not be generalizable to children from non-industrialised settings, other ethnic groups, or versions of PBD.

Several unanswered questions remain. Assuming validity of our findings regarding decreased height and BMC in vegans and vegetarians, it is unclear which aspects of PBD can contribute to these outcomes, at what age or whether supplementation or dietary change can rectify these problems. We do not know the extent and consequences of long-term cardiometabolic benefits or nutritional risks. Additional research, and replication of our findings using longitudinal studies, is desirable. Our data relate to ages 5-10 years, but the risks and benefits for children of different ages, especially infants, might vary. We propose that physicians and dieticians educate their patients on both potential benefits and risks of PBD in children, emphasizing potential effects on stature and bone associated with veganism. Vegan and vegetarian children need guidelines on how to eat healthfully, beyond advice on supplementation. Finally, current debates on PBDs and the position statements of expert organisations should focus even more on customizing the advice to vegans vs vegetarians and different age-groups so that the established benefits of these diets are maximised and the risks minimised in the pediatric population.

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TABLES

Table 1. Background characteristics by diet groups[1]

	Omnivore	**Vegetarian**	**Vegan**	***p* value**
Age (years) [2]	7.7 (1.7)	7.6 (1.6)	7.6 (1.8)	0.85[a]
Sex (boys)[3]	34 (47.2)	31 (49.2)	22 (42.3)	0.75[b]
Socioeconomic characteristics				
Residence[3]				
City	55 (76.4)	49 (77.8)	37 (71.2)	0.69[b]
Village	17 (23.6)	14 (22.2)	15 (28.8)	0.69[b]
Maternal smoking[3]	4 (5.6)	8 (12.7)	0 (0.0)	0.02[b]
Paternal smoking[3]	5 (7.0)	5 (7.9)	0 (0.0)	0.13[b]
Maternal education[3]				
Secondary	4 (5.6)	10 (15.9)	10 (19.2)	0.05[b]
Tertiary	68 (94.4)	53 (84.1)	42 (80.8)	0.05[b]
Paternal education[3]				
Secondary	16 (22.2)	20 (33.9)	14 (26.9)	0.33[b]
Tertiary	56 (77.8)	39 (66.1)	38 (73.1)	0.33[b]
Religion[3]				
None	9 (12.5)	37 (59.7)	28 (54.9)	<0.001[b]
Christian	63 (87.5)	22 (35.5)	12 (23.5)	<0.001[b]
Other	0 (0.0)	3 (4.8)	11 (21.6)	<0.001[b]
Perinatal characteristics				
Gestation age (weeks)[2]	39.0 (1.5)	39.2 (1.9)	38.8 (1.9)	0.57[a]
Birth weight (g)[2]	3415 (455)	3355 (582)	3233 (545)	0.18[a]
Maternal height (cm) [2]	167.2 (6.2)	167.1 (6.0)	168.2 (6.4)	0.55[a]
Paternal height, (cm) [2]	181.0 (7.1)	180.0 (6.1)	182.0 (7.3)	0.27[a]
Breastfeeding (m)[4,5]	12.0 (8.0, 16.5)	13.0 (7.0, 18.0)	18.0 (9.0, 24.0)	0.06[c]
Breastfed until 6m [3,5]	61 (84.7)	54 (85.7)	46 (88.5)	0.83[b]
Exclusively breastfed until 6m[3,5]	52 (72.2)	40 (63.5)	37 (71.1)	0.51[b]
Formula introduction timing[3]				
Never	24 (33.8)	28 (44.4)	31 (60.8)	< 0.001[b]

formula-fed				
1–5 months	15 (21.1)	21 (33.3)	12 (23.5)	< 0.001[b]
>= 6 months	32 (45.1)	14 (22.2)	8 (15.7)	< 0.001[b]
Maternal pre-pregnancy BMI[2]	22.5 (3.4)	21.2 (2.5)	21.9 (5.4)	0.16[a]
Maternal diet in pregnancy[3]				
Meat-eater	64 (97.0)	18 (30.0)	21 (42.0)	< 0.001[b]
Vegetarian	1 (1.5)	29 (48.3)	15 (30.0)	< 0.001[b]
Vegan	0 (0.0)	2 (3.3)	5 (10.0)	< 0.001[b]
Fish-eater	1 (1.5)	11 (18.3)	9 (18.0)	< 0.001[b]
Family history of disease				
Family history of hypertension[3]	55 (77.5)	36 (61.0)	30 (66.7)	0.12[b]
Family history of T2 diabetes[3]	22 (32.4)	14 (25.0)	13 (25.0)	0.57[b]
Family history of coronary heart disease[3]	5 (7.7)	16 (27.1)	10 (20.8)	0.02[b]
Physical activity				
Average movement count per minute[2]	8.9 (2.4)	9.2 (2.2)	9.8 (2.6)	0.17[a]
Sedentary activity (min/day)[2]	357.7 (81.7)	331.8 (76.0)	335.2 (85.6)	0.18[a]
Light activity (min./day)[2]	396.4 (61.2)	403.5 (71.5)	401.6 (67.0)	0.84[a]
Moderate activity (min/day)[2]	33.1 (16.4)	31.7 (13.9)	35.0 (14.7)	0.56[a]
Vigorous activity (min/day)[2]	9.0 (8.1)	18.8 (69.7)	10.7 (7.5)	0.40[a]
MVPA of ≥ 60 min/day[3]	10 (16)	12 (23.5)	11 (24)	0.49[b]
Fortification and supplementation practices				
Vit. B12 supplement use[3]	5 (6.9)	22 (34.9)	23 (44.2)	<0.001[b]
Vit. B12 fortified products use[3]	17 (23.6)	38 (60.3)	34 (65.4)	<0.001[b]
No Vit. B12 supplement and no B12 fortification use[3]	52 (72.2)	17 (27)	15 (29)	<0.001[b]
Vit. D supplement use[3]	27 (37.5)	21 (33.3)	17 (32.7)	0.82[b]

[1]Omnivores n=72, vegetarians n=63, vegans n=52; [2]values are means (SDs); [3]values are N (%); [4]values are medians (IQR); [5]months; ANOVA (means)[a], chi-square test (percentages)[b] and Kruskall-Wallis test (median)[c] were used to test the null hypothesis of no difference between the groups, MVPA- moderate & vigorous physical activity.

Table 2. Crude and adjusted mean differences of vegetarian and vegan children relative to omnivore children in anthropometry and body composition[1]

Outcome	Model 1[2]		Model 2[3]	
	Vegetarian	Vegan	Vegetarian	Vegan
	Δ[4] (95% CI)	Δ (95% CI)	Δ (95% CI)	Δ (95% CI)
Height *z*-score	**-0.45 (-0.77, -0.12)[5]**	**-0.55 (-0.97, -0.12)**	-0.32 (-0.68, 0.03)	**-0.57 (-1.02, -0.12)**
BMI *z*-score	-0.24 (-0.54, 0.06)	-0.50 (-0.82, -0.17)	-0.31 (-0.64, 0.02)	**-0.53 (-0.95, -0.12**)
Lean mass index *z*-score	0.018 (-0.279, 0.315)	0.198 (-0.134, 0.531)	-0.066 (-0.414, 0.281)	0.073 (-0.321, 0.468)
Fat mass index *z*-score	-0.33 (-0.68, 0.01)	-**0.78 (-1.14, -0.42)**	-0.29 (-0.65, 0.07)	**-0.72 (-1.12, -0.32)**
Biceps skinfold *z*-score	0.03 (-0.21, 0.27)	-0.23 (-0.5, 0.06)	0.04 (-0.28, 0.36)	-0.16 (-0.56, 0.23)
Suprailiac skinfold *z*-score	-0.0 (-0.35 0.23)	**-0.49 (-0.79, -0.19)**	-0.13 (-0.45, 0.2)	**-0.57 (-0.97, -0.18)**
Subscapular skinfold *z* -score	0.08 (-0.20, 0.36)	-0.31 (-0.64, 30.03)	0.11 (-0.23, 0.45)	-0.23 (-0.68, 0.22)
Triceps skinfold *z*-score	-0.13 (-0.43, 0.17)	-0.56 **(-0.87, -0.24)**	-0.11 (-0.48, 0.26)	**-0.47 (-0.86, -0.09)**
Waist girth *z* -score	-0.24 (-0.52, 0.04)	-0.23 (-0.51, 0.05)	-0.28 (-0.61, 0.05)	-0.30 (-0.67, 0.08)
Hip girth *z*-score	-0.20 (-0.53, 0.13)	-**0.59 (-0.86, -0.31)**	-0.13 (-0.56, 0.29)	**-0.58 (-0.94, -0.21)**
Thigh girth *z*-score	-0.37 (-0.65, -0.09)	-**0.61 (-0.90, -0.31)**	**-0.37 (-0.69, -0.05)**	**-0.58 (-0.97, -0.20)**

[1]Ranges of participants available for each outcome by diet group were as follows: omnivores – 67-72, vegetarians – 62-63, vegans – 45-52; [2]Model 1**:** diet group only; [3]Model 2**:** diet group, maternal height, paternal height, birthweight (fifths), gestational age (fifths), maternal pre-pregnancy BMI (fifths), average movement count per hour internal z-score, breastfeeding duration (<6, 6-12, >12 months), maternal education, paternal education, area of residence; multiple imputation was used to account for missing data; [4]difference; [5]bold font indicates statistical significance at p-value < 0.05. Linear regression was used to test the null hypothesis of no difference between vegetarian and omnivore, and vegan and omnivore groups.

Table 3. Crude and adjusted mean differences of vegetarian and vegan children relative to omnivore children in bone, cardiovascular and body iron status outcomes

Outcome group	Vegetarian	Vegan	Vegetarian	Vegan	Vegetarian	Vegan
	Δ[2] (95% CI)	**Δ (95% CI)**	**Δ (95% CI)**	**Δ (95% CI)**	**Δ (95% CI)**	**Δ (95% CI)**
Bone status[1]	**Model 1[3]**		**Model 2[4]**		**Model 3[5]**	
TBLH BMC (%)[6]	**-7.8[7] (-13.6, -2.1)**	**-16.4 (-24.4, -8.4)**	**-7.3 (-14.3, -0. 2)**	**-15.2 (-25.4, -4.9)**	11 (-1.6, 3.8)	**-3.7 (-7.0, -0.4)**
L2-4 BMC (%)[6]	**-5.3 (-10.5, 0.0)**	**-10.5 (-17.1, -3.9)**	-4.6 (-10.5, 1.3)	**-9.3 (-17.6, -1.1)**	-0.05 (-4.6, 3.7)	**-5.6 (-10.6, -0.5)**
BMAD *z*-score	-0.086 (-0.408, .237)	**-0.652 (-1.052, -0.253)**	-0.056 (-0.465, 0.353)	**-0.615 (-1.099, -0.132)**	., .	., .
BMAD %ile	-3.3 (-11.5, 4.9)	**-12.6 (-21.8, -3.4)**	-2.2 (-12.5, 8.1)	**-11.3 (-22.4, -0.2)**	., .	., .
Cardiovascular risk[8]	**Model 1[2]**		**Model 2[9]**		**Model 3[10]**	
Insulin (µUl/mL)	0.23 (-0.56, 1.03)	-0.04 (-0.86, 0.78)	0.20 (-0.84, 1.24)	-0.02 (-1.16, 1.12)	0.56 (-0.39, 1.50)	0.69 (-0.31, 1.70)
Fasting glucose (mg/dL)	**3.2 (1.0, 5.5)** [6]	2.2 (-0.1, 4.6)	**3.1 (0.9, 5.4)**	1.9 (-1.0, 4.8)	**3.6 (1.4, 5.8)**	2.7 (-0.3, 5.7)
HOMA-IR (%)[6]	9.1 (-2.4, 20.6)	4.7 (-8.2, 17.5)	8.6 (-6.2, 23.4)	4.5 (-11.7, 20.6)	**14.1 (0.8, 27.4)**	**14.9 (0.1, 29.7)**
Total cholesterol (mg/dL)	-9.3 (-19.2, 0.5)	**-33.6 (-42.6, -24.6)**	**-11.5 (-22.4, -0.6)**	**-35.6 (-48.3, -22.9)**	-10.2 (-21.2, 0.9)	**-32.1 (-45.1, -19.0)**
HDL-cholesterol (mg/dL)	**-5.0 (-9.5, -0.5)**	**-10.6 (-14.7, -6.4)**	**-6.5 (-11.1, -1.8)**	**-12.2 (-17.3, -7.1)**	**-6.8 (-11.6, -2.0)**	**-12.7 (-18.2, -7.1)**
LDL-cholesterol (mg/dL)	-6.2 (-14.4, 2.0)	**-23.4 (-31.0, -15.7)**	-6.9 (-15.6, 1.8)	**-24.0 (-35.2, -12.9)**	-5.5 (-14.4, 3.3)	**-20.5 (-31.8, -9.2)**
VLDL-cholesterol (%)[6]	**14 (3.0, 25.0)**	**0.0 (-13.0, 14.0)**	**14.0 (1.0, 28.0)**	2.0 (-15.0,18.0)	**16.0 (2.0, 30.0)**	6.0 (-12.0, 23.0)
Triglycerides (%)[6]	**18.0 (6.0, 29.0)**	3.0 (-12.0, 17.0)	**19.0 (5.0, 33.0)**	6.0 (-12.0, 24.0)	**22.0 (7.0, 36.0)**	11.0 (-8.0, 29.0)
hsCRP (%)[6]	-22.0 (-57.0, 14.0)	**-47.0 (-80.0, -15.0)**	-38.0 (-81.0, 5.0)	**-81 (-123.0, -39.0)**	-34.0 (-80.0, 11.0)	**-72.0 (-118.0, -26.0)**
cIMT (mm)	0.000 (-0.010, 0.010)	-0.008 (-0.022, 0.006)	-0.001 (-0.013, 0.011)	-0.009 (-0.024, 0.007)	0.000 (-0.012, 0.013)	-0.007 (-0.021, 0.008)
IGFBP3 (ng/mL)	65 (-150, 280)	-105 (-348, 139)	43 (-205, 290)	-144 (-437, 150)	105 (-125, 335)	-50 (-317, 217)
IGF-1 (ng/mL)	-14 (-45, 16)	-14 (-46, 17)	-10 (-43, 24)	-7 (-47, 34)	6 (-24, 35)	20 (-14, 53)
Molar IGF1:IGFBP3 ratio	-0.020,(-0.045, 0.004)	-0.014, (-0.040, 0.011)	-0.016 (-0.044, 0.012)	-0.006 (-0.038, 0.027)	-0.005 (-0.030, 0.020)	0.014 (-0.015, 0.042)
hsCRP values <1 (%) [6]	-5.8 (-36.5, 25.0)	**-32.0 (59.6, -4.0)**	-15.4 (-52.2, 21.4)	**-55.9 (-90.4, -21.4)**	-10.5 (-48.8, 27.8)	**-44.9 (-81.7, -8.0)**

Body iron status[11]	**Model 1**[2]		**Model 2**[12]		-	
RBC (M/µl)	-0.09 (-0.18, 0.01)	**-0.23 (-0.33, -0.12)**[5]	-0.07 (-0.17, 0.02)	**-0.23(-0.33, -0.12)**	-	-
HGB (g/dL)	-0.24 (-0.50, 0.02)	**-0.38 (-0.70, -0.06)**	-0.20 (-0.47, 0.07)	**-0.37 (-0.69, -0.05)**	-	-
HTC (%)	**-83.0 (-160.0, -7.0)**	**-105.0 (-203.0, -8.0)**	-72.0 (-150.0, 7.0)	**-105.0 (-204.0, -5.0)**	-	-
Ferritin[6] **(%)**	**-19.0 (-37.0, -1.0)**	**-28.0 (-48.0, -7.0)**	-14.0 (-32.0, 3.0)	**-25.0 (-44.0, -5.0)**	-	-

[1]Ranges of participants available for each outcome by diet group were as follows: omnivores – 71-72, vegetarians – 62-63, vegans 52 (no missing outcome data); [2] difference; [3]Model 1**:** diet group, age, sex; [4]Model 2**:** diet group, age, sex, maternal education, religion, urbanicity; [5]Model 3**:** diet group, age, sex, maternal education, religion, urbanicity, height z-score (UK), weight z-score (UK), bone area; [6]variable log-transformed, results represent percent difference; [7]bold font indicates statistical significance at p-value < 0.05; [8]ranges of participants available for each outcome by diet group were as follows: omnivores – 68-71, vegetarians – 60-62, vegans 52 (no missing outcome data); [9]Model 2**:** diet group, age, sex, birthweight quintile, gestational age quintile, maternal pre-pregnancy BMI quintile, breastfeeding at 6, 6-12 and over 12 months, maternal education, paternal education, religion, urbanicity;[10]Model 3**:** diet group, age, sex, birthweight quintile, gestational age quintile, maternal pre-pregnancy BMI quintile, breastfeeding at 6, 6-12 and over 12 months, maternal education, paternal education, religion, urbanicity, height z-score (UK), fat mass z-score (DXA), lean mass z-score (DXA), [11]Omnivores n=72, vegetarians n=62, vegans n=52; [12]Model 2**:** diet group, age, sex, maternal education, urbanicity, maternal smoking. Linear regression was used to test the null hypothesis of no difference between vegetarian and omnivore, and vegan and omnivore groups. TBLH BMC - total body less head bone mineral content; L2-L4 - lumbar spine L2-L4 bone mineral content; BMAD - bone apparent mineral density; cIMT-carotid intima media thickness; hs-CRP -high sensitivity C-reactive protein; IGF-1-insulin growth factor 1; IGFBP3- insulin growth factor binding protein 3.

Table 4. Crude and adjusted mean differences of vegetarian and vegan children relative to omnivore children in serum vitamin B12, homocysteine and MCV concentrations addressing variation in vitamin B12 supplementation and fortification practices[1]

Outcome	Vegetarian - no supplementation or fortification	Vegetarian – fortification only	Vegetarian – supplementation and fortification	Vegan – no supplementation or fortification	Vegan – fortification only	Vegan – supplementation and fortification
	Δ[3] **(95% CI)**	Δ **(95% CI)**	Δ **(95% CI)**	Δ **(95% CI)**	Δ **(95% CI)**	Δ **(95% CI)**
Model 1[2]						
Vit. B12 (pmol/L)	**-61.1 (-114.7, -7.6)**[4]	2.1 (-69.6, 73.7)	85.9 (-6.1, 177.9)	**-183.8 (-251.9, -115.8)**	**-104.0 (-192.0, -16.0)**	66.9 (-36.0, 169.9)
Homocysteine[5] (%)	**14.0 (0.0, 27.0)**	-5.0 (-15.0, 4.0)	**-12.0 (-25.0, 0.0)**	**48.0 (25.0, 72.0)**	14.0 (-8.0, 36.0)	-10.0 (-24.0, 3.0)
MCV (fl)	-0.28 (-2.16, 1.61)	-0.06 (-2.10, 1.98)	-0.63 (-2.58, 1.33)	**4.25 (1.35, 7.15)**	0.84 (-1.64, 3.32)	0.91 (-0.65, 2.46)
Model 2[6]						
Vit. B12 (pmol/L)	**-90.9 (-156.7, -25.1)**	- 26.4 (-101.5, 48.7)	68.1 (-37.4, 173.6)	**-217.6 (-305.7, -129.5)**	**-139.8 (-235.3, -44.3)**	43.5 (-59.3, 146.4)
Homocysteine[5] (%)	**15.0 (0.0, 30.0)**	-2.0 (-14.0, 9.0)	-11.0 (-25.0, 2.0)	**50.0 (27.0, 74.0)**	16.0 (-8.0, 40.0)	-9.0 (-24.0, 6.4)
MCV (fl)	-0.28 (-2.33, 1.76)	-0.07 (-2.39, 2.24)	-0.61 (-2.67, 1.46)	**4.19 (1.19, 7.18)**	0.97 (-1.63, 3.58)	0.83 (-0.99, 2.64)

[1] Omnivores n=71-72, vegetarians - no supplementation or fortification n=17, vegetarian – fortification only n=23, vegetarian – supplementation and fortification n=22, vegan – no supplementation or fortification n=15, vegan – fortification only n=14, vegan – supplementation and fortification n=23; [2] Model 1**:** dietary group categorised according to supplementation and fortification status;[3] difference; [4] bold font indicates statistical significance at p-value < 0.05; [5] variable log-transformed; results represent percent difference;[6] Model 2**:** dietary group categorised according to supplementation and fortification status, maternal education, religion. Linear regression was used to test the null hypothesis of no difference between vegetarian and omnivore, and vegan and omnivore groups.

Table 5. Crude and adjusted mean differences of vegetarian and vegan children relative to omnivore children in serum D 25 (OH) concentrations addressing variation in vitamin D supplementation practices[1]

Outcome	Vegetarian - no supplementation	Vegetarian - supplementation	Vegan - no supplementation	Vegan - supplementation
	Δ[2] (95% CI)	**Δ (95% CI)**	**Δ (95% CI)**	**Δ (95% CI)**
Model 1[3]				
Serum D 25 (OH) nmol/L	**-7.1 (-13.7, -0.4)[4]**	**9.2 (0.7, 17.7)**	**-13.2 (-20.2, -6.3)**	-2.5 (-11.5, 6.6)
Model 2[5]				
Serum D 25 (OH) nmol/L	**-7.1 (-13.8, -0.3)**	**9.2 (0.6, 17.7)**	**-13.3 (-20.3, -6.2)**	-2.5 (-11.6, 6.6)

[1] Omnivores n=72, vegetarian - no supplementation n=40, vegetarian – supplementation n=20, vegan - no-supplementation n=35, vegan - supplementation n=17; [2] difference, [3] Model 1**:** dietary group categorised according to supplementation status, age, sex, seasonality (sine and cosine function of the day of the year of blood draw); [4] bold font indicates statistical significance at p-value < 0.05; [5] Model 2**:** dietary group categorised according to supplementation status, age, sex, seasonality (sine and cosine function of the day of the year of blood draw), maternal education. Linear regression was used to test the null hypothesis of no difference between vegetarian and omnivore, and vegan and omnivore groups. D25 (OH) -25 hydroxy vitamin D.

Table 6. Estimated prevalence of inadequate vitamin B12, iron and cholesterol status[1]

Outcome	Omnivore	Vegetarian	Vegan
Vitamin B12			
Probable deficiency (<148 pmol/L)	3.2 (0.3, 6.0)	3.8 (0.8, 6.8)	**13.0 (2.6, 23.4)** [2]
Possible deficiency (≥148–258 pmol/L)	16.5 (7.5, 25.6)	19.2 (10.2, 28.2)	**39.9 (27.8, 52.0)**
Hemoglobin			
Moderate deficiency (8.00-10.9 g/dl)	0	1.9 (-0.3,4.1)	1.6 (-1.3, 4.5)
Mild deficiency (11.0–11.4 g/dl)	0	6.6 (-0.02, 13.3)	**5.6 (1.0,10.2)**
Ferritin			
Depleted iron stores (< 15 µg/l)	12.8 (0.05, 20.2)	18.3 (8.5, 28.1)	**30.2 (16.2, 44.3)**
LDL cholesterol			
High (≥130 mg/dL)	13.3 (2.2, 24.5)	5.7 (1.1, 10.2)	**0.4 (-0.4, 1.2)**
Borderline (110–129 mg/dL)	17.0 (9.2, 24.9)	9.7 (4.1, 15.2)	**0.9 (-1.0, 2.7)**
Acceptable (<110 mg/dL)	69.6 (55.2, 84.0)	84.7 (76.4, 92.9)	**98.7 (96.1, 101.3)**
HDL cholesterol			
Acceptable (>45 mg/dL)	81.3 (70.7, 91.9)	65.9 (53.9, 78.0)	**49.2 (34.3, 64.1)**
Borderline (40–45 mg/dL)	11.8 (5.4, 18.1)	19.3 (12.2, 26.4)	**24.4 (16.5, 32.4)**
Low (<40 mg/dL)	6.9 (1.6, 12.1)	14.8 (6.9, 22.8)	**26.4 (14.0, 38.7)**

[1]Values are expressed as percentages (95%CI); omnivores n=72, vegetarians n=62, vegans n=51 (52 for hemoglobin and ferritin); [2]bold font indicates that pairs of estimated prevalences in vegetarians or vegans and the reference group of omnivores are significantly different at p-value < 0.05. Pairwise comparisons of marginal predictions following ordinal logistic regression were used to test the null hypothesis of no difference between vegetarian and omnivore, and vegan and omnivore groups. The following covariates were included in the models: vitamin B12 – maternal education, urbanicity, maternal smoking; hemoglobin and ferritin – maternal education, religion; LDL and HDL cholesterol: birthweight quintile, gestational age quintile, maternal pre-pregnancy BMI quintile, breastfeeding at 6, 6-12 and over 12 months, maternal education, paternal education, religion, urbanicity.

Legends for illustrations

Figure 1. Flow diagram of study from recruitment to inclusion.