1 **Original article – Clinical and Population Research**
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4 **Inflammatory diet and preclinical cardiovascular phenotypes in 11-12 year-olds and**
5 **mid-life adults: A cross-sectional population-based study**

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ABSTRACT

Background and aims: Pro-inflammatory diet may be a modifiable risk factor for cardiovascular disease. We examine associations of two inflammatory diet scores with preclinical cardiovascular phenotypes at two lifecourse stages.

Methods: *Participants:* 1,771 children (49% girls) aged 11-12 years and 1,793 parents (87% mothers, mean age 43.7 (standard deviation 5.2) years) in the Child Health CheckPoint Study. *Measures:* 23 items in the Australian National Secondary Students' Diet and Activity (NaSSDA) survey were used to derive two inflammatory diet scores based on: 1) published evidence of associations with C-reactive protein (literature-derived score), and 2) empirical associations with CheckPoint's inflammatory biomarker (glycoprotein acetyls, GlycA-derived score). Cardiovascular phenotypes assessed vascular structure (carotid intima-media thickness, retinal vessel calibre) and function (pulse wave velocity, blood pressure). *Analyses:* Linear regression models were conducted, adjusted for age, sex, socioeconomic position and child pubertal status, plus a sensitivity analysis also including BMI (z-score for children).

Results: In adults, both inflammatory diet scores showed small associations with adverse cardiovascular function and microvascular structure. Per standard deviation higher GlycA-derived diet score, pulse wave velocity was 0.17m/s faster (95% CI 0.11 to 0.22), mean arterial pressure was 1.85mmHg (1.34 to 2.37) higher, and retinal arteriolar calibre was 1.29µm narrower (-2.10 to -0.49). Adding BMI to models attenuated associations towards null. There was little evidence of associations in children.

Conclusions: Our findings support cumulative adverse effects of a pro-inflammatory diet on preclinical cardiovascular phenotypes across the lifecourse. Associations evident by mid-life were not present in childhood, when preventive measures should be instituted.

Keywords: Diet, Inflammation, Cardiovascular Health, Child, Adult, CheckPoint

INTRODUCTION

Inflammation is a central pathogenic mechanism and therapeutic target in atherosclerosis.[1] A pro-inflammatory diet is considered a modifiable risk factor for atherosclerotic cardiovascular disease (CVD),[2-4] and western diets have a particularly high pro-inflammatory potential.[5] Specific food groups, such as refined carbohydrates, red/processed meat and sugar-sweetened beverages, are suggested to promote inflammation.[6] Others, such as fish, fruit, vegetables, and low or non-fat dairy sources, have demonstrated anti-inflammatory effects in both animal and human studies.[7] However, investigating only the pro- or anti-inflammatory elements of diets neglects potential synergistic and antagonistic interactions.

The Dietary Inflammatory Index (DII) is widely used to capture both pro- and anti-inflammatory dietary patterns.[8] In adulthood, higher (i.e. pro-inflammatory) DII scores predict CVD events. Two large meta-analyses including prospective and cross-sectional studies of adults aged 38-69 years from the general population reported that those in the highest DII category, compared to the lowest, had a 20-30% increased risk of cardiovascular mortality and disease.[2, 9] A pro-inflammatory diet is also associated with increased cardiovascular risk in early to mid-adulthood. For example, two recent NHANES studies demonstrated that a) among 7,880 adults aged ≥20 years (mean age ranged 35-51 years), higher DII scores were associated with increased prevalence of obesity, diabetes, hypertension and hypercholesterolemia,[10] and b) among 17,689 adults (mean age 47 years), the odds of higher blood pressure and other cardiometabolic risk factors increased across DII quintiles.[11] Smaller European cohorts report similar results for blood pressure.[4]

Cardiovascular risk develops across the lifecourse, with childhood a key period for primordial prevention.[12] In 6-24 year-olds, diet quality is clearly associated with dietary anti-inflammatory potential measured by the DII,[13] but very little research has directly examined

the relationship between children's inflammatory diets and cardiovascular risk factors and

preclinical phenotypes. One recent community-based study reported that children's DII

scores were associated with their waist-to-height ratio, but not with body composition, blood

pressure or heart rate.[14] Therefore, it is still unknown whether the adverse associations seen

in adult studies are already evident in childhood, when early atherosclerosis develops and

when adverse risk trajectories are established.[15] We therefore aimed to examine associations

of inflammatory diet scores with preclinical phenotypes of cardiovascular structure (carotid

intima-media thickness, retinal vessel calibre) and function (pulse wave velocity, blood

pressure) in population-based cohorts of 11-12 year-olds and mid-life adults.

MATERIALS AND METHODS

Study design and participants

The Child Health CheckPoint study (CheckPoint) was a cross-sectional population-based

study nested within the national Longitudinal Study of Australian Children (LSAC). LSAC's

initial study design and recruitment are outlined elsewhere.[16] Briefly, LSAC recruited a

nationally-representative birth (B) cohort of 5,107 infants at age 0-1 years using a two-stage

random sampling design, with biennial 'waves' of data collection thereafter.[17] CheckPoint

was a detailed cross-sectional biophysical assessment, nested between LSAC's 6th and 7th

waves from February 2015 to March 2016. Of the 3764 (74%) families retained at wave 6,

3,513 (93%) consented to their contact details being shared with the CheckPoint team.

CheckPoint's study design and methods are outlined in detail elsewhere,[18] and the procedures

and measures germane to this study are outlined below. Informed consent for each child was

provided by a parent/guardian. The Royal Children's Hospital (HREC33225) and the

Australian Institute of Family Studies (AIFS14-05) Ethics Committees approved the study.

1

Procedures

3 Most participants attended a 3.5 hour Main or 2.5 hour Mini Assessment Centre in one of

4 Australia's capital cities or large regional towns, where they rotated through a series of 15-

5 minute physical assessment and biospecimen collection stations. Participants unable to attend

6 a centre were offered a 90-minute home visit. We draw on data collected from all three types

7 of assessments, although one cardiovascular measure was omitted at Mini Assessment

8 centres and two measures at home visits (see below).

9

Measures

11 We draw on measures from CheckPoint and LSAC's wave 1 to 6.

Inflammatory diet scores

13 Self-reported dietary intake was collected via iPad using REDCap (Research Electronic Data

14 Capture), a secure web-based application. Children and adults separately completed a subset

15 of 26 questions from a standardised food frequency questionnaire, modified from the

16 National Secondary Students' Diet and Activity (NaSSDA) survey.[19] The NaSSDA was

17 designed to monitor Australian secondary students' diet, food marketing exposure and

18 physical activity, yet CheckPoint only assessed the diet-related items. Participants reported

19 their usual daily or weekly intake of a range of foods and drinks, including fruit, vegetables,

20 confectionary, red meat, fish and fruit juice. The level of detail precluded calculating a DII

21 for participants. Therefore we used each relevant NaSSDA item to derive two CheckPoint

22 inflammatory diet scores: 1) a score derived from published literature (the literature-derived

23 score), and 2) a GlycA-derived score based on the statistical correlation between each dietary

1   survey item and levels of the inflammatory biomarker (glycoprotein acetyls, GlycA).[20] For

2   both scores, we excluded three NaSSDA items related to breakfast skipping, breakfast cereal

3   and diet drink intake, as the nutritional content of breakfast cereal items are highly variable

4   and the inflammatory potential of diet drinks or skipping breakfast is uncertain.[6]

5   The *literature-derived inflammatory diet score* was guided by two highly cited systematic

6   reviews[21, 22] that determined the 'inflammatory potential' of different food and beverage

7   components in adults from their predicted effects on C-reactive protein (CRP), a known

8   biomarker of inflammation. We categorised each NaSSDA item as either anti-inflammatory

9   (e.g. fish consumption) or pro-inflammatory (e.g. red meat consumption) from their reported

10   associations with CRP. We then assigned each item's response options a value from -2 (anti-

11   inflammatory) to +2 (pro-inflammatory). Finally, we summed all items to generate an overall

12   literature-derived inflammatory diet score for each participant ranging from -6 to +29, where

13   higher scores indicate a more pro-inflammatory diet. Table 1 details scoring for each

14   NaSSDA item.

15   The *GlycA-derived inflammatory diet score* was based on an inflammatory biomarker,

16   GlycA, measured in CheckPoint. As only adult data thus far support GlycA as a marker of

17   chronic inflammation,[20, 23] we created the GlycA-derived score for the adults in our cohort

18   and then applied it to the children. GlycA was measured from semi-fasting plasma (only

19   collected at Main Assessment centres) by nuclear magnetic resonance (Nightingale, Helsinki,

20   Finland), as previously described.[24] GlycA values were highly positively skewed, so these

21   values were natural-log-transformed to meet assumptions of normality for linear regression

22   analyses. Adult responses to each of the NaSSDA items were individually regressed against

23   their GlycA values. Twenty of 23 univariable associations reached a statistical significance

24   level of $p<0.20$,[25, 26] Fourteen of these 20 NaSSDA items remained associated with GlycA

25   ($p<0.20$) in a combined multivariable model, and were entered into a final multivariable

1   model (Table 1). Coefficients from this final model were then used to generate an

2   inflammatory diet score for each adult with the following formula:

3   *"sum (model β for item x * participants' NaSSDA item x response value) + "model*

4   *constant".*

5   This same formula was used to create the GlycA-derived score for children with NaSSDA

6   data. Higher scores on the GlycA-derived score indicate a more pro-inflammatory diet.

7   ***Preclinical cardiovascular phenotypes***

8   Detailed methods for each cardiovascular preclinical phenotypes are described elsewhere,[24,]

9   [27-29] and are briefly described here.

10   ***Vascular function:*** *Pulse wave velocity (PWV)* and *blood pressure* were assessed using the

11   SphygmoCor XCEL device (AtCor medical, Sydney, NSW, Australia). Data were collected

12   after several minutes of rest in the supine position three times and the mean calculated from

13   at least two valid measurements. PWV was measured between the right carotid and femoral

14   artery using tonometry, providing an estimate of large arterial function, with quicker scores

15   representing greater arterial stiffness. *Systolic* and *diastolic blood pressure* and *mean arterial*

16   *pressure* parameters were measured at the right brachial artery using an appropriately sized

17   cuff.

18   ***Vascular structure:*** *Carotid intima-media thickness* (carotid IMT) was assessed at Main and

19   Mini Assessment Centres via B-mode ultrasound (Vivid-I BT06 with 10MHz L-RS Vascular

20   probe, GE Healthcare, Chicago, IL, USA) of the right common carotid artery. Subjects were

21   in the supine position and head rotated left 45 degrees. A modified 3-lead ECG mapped the

22   cardiac cycle, and sonographic images of a minimum of three longitudinal loops of 5-10

23   cardiac cycles were taken 10mm proximal to the carotid bulb. Image analysis using semi-

24   automated edge-detection software (Carotid Analyser, Medical Imaging Applications,

1 Coraville, IA, USA) calculated carotid IMT far wall mean, with higher scores representing

2 poorer cardiovascular structure. The within-observer and between-observer coefficients of

3 variation were 6.5% and 9.5% for mean carotid IMT values, respectively.[30] Reliability was

4 comparable to other published results.[31] *Retinal vessel calibre* was assessed at Main

5 Assessment centre only via digital photographs of the optic disc in the right eye using CR-

6 DGi fitted with an EOS 60D SLR digital camera (Canon Inc., Tokyo, Japan) by trained

7 technicians. Computer-assisted retinal analysis software IVAN (University of Wisconsin,

8 Madison, WI, USA) measured vessel calibre. Using the Big-6 method,[32] graders estimated

9 central retinal arteriolar (higher scores = better) and venular calibre (higher score = worse).

10 Inter- and intra-grader intraclass correlation coefficients between graders ranged from 0.76 to

11 0.99, indicating high reproducibility.[29]

12 *Potential confounders*

13 Potential confounders included age, sex, socioeconomic position and (in children only)

14 pubertal status, as well as children's arterial diameter in carotid IMT analyses.

15 Socioeconomic position was calculated from the most recently available parent-reported

16 education, income and occupation data at LSAC's wave 6. Scores were internally

17 standardised to have a mean of 0 and standard deviation (SD) of 1; higher scores represent

18 higher socioeconomic position,[33] which has been strongly linked with higher cardiovascular

19 risk[30] and poor diet.[34] Pubertal status was calculated from self-reported ratings of secondary

20 sexual characteristics and growth using the 5-item Pubertal Development Scale.[35] Early

21 puberty is associated with poorer long-term health outcomes.[36] For carotid IMT analyses, we

22 also adjusted for children's minimal vessel diameter to account for differences in body and

23 vessel size during growth.

24 *Sensitivity analysis variables*

1 Body mass index (BMI; weight/height^2) for adults and children (z-score, standardised for age

2 and sex, calculated from US Centers for Disease Control (CDC) reference values[37]) were

3 included in a sensitivity analysis. BMI is strongly linked to both poor dietary patterns and

4 cardiovascular risk,[38] so could plausibly lie on the causal pathway between inflammatory

5 diets and preclinical cardiovascular phenotypes. Further sensitivity analyses excluded adults

6 who self-reported current blood pressure and/or cholesterol lowering medication, and those

7 with a prior heart condition.

8 *Additional descriptive variables*

9 We were able created a binary variable of "ever exposed to passive smoke" for children or

10 "smoked in the previous decade" for adults from the LSAC questionnaire data. This variable

11 was positive if the answer in any of the six LSAC waves prior to CheckPoint (ages 0-1 to 10-

12 11 years) was >0.

13 **Statistical analysis**

14 All data were analysed using Stata version 14.2. For this cross-sectional study, we

15 conceptualised the two inflammatory diet scores as "risk factors" and preclinical

16 cardiovascular phenotypes as "outcomes". Participants were included if they completed the

17 NaSSDA and had at least one cardiovascular measure.

18 Linear regression assumptions were tested when fitting models to assess associations of

19 inflammatory diet scores with preclinical cardiovascular phenotypes in children and adults

20 Unadjusted and adjusted linear regression models estimated associations of inflammatory diet

21 scores with preclinical cardiovascular phenotypes. Both inflammatory diet scores were

22 internally standardised to have a mean of zero and SD of one. Adjusted models included age,

23 sex, socioeconomic position and pubertal status (children only). Child carotid IMT analyses

24 were additionally adjusted for minimal vessel diameter. We also performed two sensitivity

1 analyses: 1) including BMI/BMI z-score, 2) including passive smoking exposure and 3)

2 excluding adults taking blood pressure or cholesterol lowering medication and/or with a prior

3 heart condition.

4 Finally, interaction tests were performed to assess for differential sex associations, which

5 may be of particular relevance in adults given sex-specific differences in cardiovascular

6 risk.[39]

7

RESULTS

8 **RESULTS**

9 **Sample characteristics**

10 Of the 3,764 eligible families, 1,875 (47% of LSAC wave 6) child-parent pairs participated in

11 CheckPoint. Dietary and preclinical cardiovascular phenotypes were available for 1,771

12 children and 1,793 adults. Figure 1 shows the flow through the study, including the numbers

13 with each of the vascular function and structure measures.

14 On average, children and adults were aged 11.5 (SD: 0.5) and 43.7 (SD: 5.2) years,

15 respectively, and adults were predominantly female (87.7%, children 49.5% female; Supp

16 Table 1)). The socioeconomic position of the analytic sample was 0.2 SD units higher than

17 the national Australian average, indicating a slightly more advantaged population. Most

18 children were in early to mid-puberty (77%), and children and adults had similar levels of

19 overweight (15% and 33%) and obesity (9% and 29%) to current Australian norms.[40]

20 A total of 8% of adults self-reported either having a heart condition, high blood pressure or

21 taking high cholesterol or blood pressure medication. Smoked in the past decade or exposure

22 to passive smoke in the household over the preceding decade was reported in 15% and 16%

23 of adults and children, respectively. Children and adult's average literature-derived diet

1   scores were 2.50 (SD 3.04; range:-5 to 14) and 0.77 (2.46; -5 to 13), and their GlycA-derived

2   scores were 0.065 (SD 0.063; -0.14 to 0.42) and 0.025 (SD 0.057; -0.15 to 0.35),

3   respectively.

4   **Associations of inflammatory diet scores with preclinical cardiovascular phenotypes**

5   Given their similarity to the unadjusted models for both children and middle-aged adults, we

6   present adjusted results only.

7   In children, there was little evidence to suggest that either inflammatory diet score was

8   associated with cardiovascular structural or functional phenotypes (Table 2).

9   In adults, there was modest statistical evidence that both inflammatory diet scores were

10   associated with worse cardiovascular function (Table 3). For example, per SD higher GlycA-

11   derived diet score, pulse wave velocity was 0.17 m/s faster (95% confidence interval (CI)

12   0.11 to 0.22), systolic and diastolic blood pressure was1.65 (95% CI 1.02 to 2.28) and 1.36

13   (95% CI 0.92 to 1.80) mmHg higher respectively, mean arterial pressure was 1.85 mmHg

14   (95% 1.34 to 2.37) higher, and retinal arteriolar calibre was 1.29 µm narrower (-2.10 to -

15   0.49). These associations were small, representing only 0.1-0.2 SD effect sizes for the

16   cardiovascular function measures. Results were similar, although, smaller for literature-

17   derived inflammatory diet scores. When BMI was added to the models, these associations

18   were attenuated partially for the GlycA-derived and fully for the literature-derived

19   inflammatory diet scores.

20   There was little evidence to suggest that inflammatory diet scores were associated with

21   carotid IMT or retinal venular calibre in adults. However, higher inflammation on both diet

22   scores was consistently associated with narrower (worse) retinal arteriolar calibre. Thus, per

23   SD higher GlycA-derived and literature-derived inflammatory diet score, arteriolar calibre

24   narrowed 1.29µm (95% CI -2.10 to -0.49) and 1.20µm (95% CI -2.01 to -0.39) respectively.

1   Again, these effect sizes were small (less than 0.1 SD). When BMI was added these

2   associations attenuated, and a new association between the GlycA-derived inflammatory

3   score and carotid IMT emerged.

4   Excluding the 8% of adults taking blood pressure or cholesterol lowering medication, and/or

5   with a prior heart condition, made little difference to the results. Similarly, interaction tests

6   did not provide statistical evidence to suggest that associations differed by sex in children or

7   adults (data not shown).

8

9   **DISCUSSION**

10   **Principal findings**

11   In children aged 11-12 years, there was little evidence that an inflammatory diet was

12   associated with preclinical phenotypes of either vascular function or structure. By mid-life, a

13   pro-inflammatory diet was consistently associated with adverse variations in vascular

14   function (all measures) and microvascular structure (i.e. retinal arteriolar calibre). These

15   associations were small, butare likely to worsen with cumulative exposure to an

16   inflammatory diet. All associations were stronger for the GlycA-derived than the literature-

17   derived inflammatory diet score, and attenuated towards the null when BMI was added to the

18   models.

19   **Interpretation in relation to previous research**

20   To our knowledge, no studies have thoroughly examined the relationship between

21   inflammatory diet scores and multiple preclinical cardiovascular phenotypes in a mid-life

22   population cohort. Our observed associations in mid-life adults are in the same direction as

23   reported associations between the DII and single cardiovascular risk factors (e.g. blood

24   pressure) and disease in mid-late adulthood,[2, 4, 9-11] but their magnitude was notably smaller.

Similar to our results, previous studies of community/population cohorts have shown that in comparison to mid-life adults in the lowest DII category, those in the highest category have slightly higher blood pressure.[4, 10, 11] Although this finding was not replicated in a similar study with adults ranging from early- to late-life.[41] Meta-analytic results (n=534,906) from both clinical trials and epidemiological studies also demonstrate that adherence to the anti-inflammatory Mediterranean dietary pattern has beneficial effects on blood pressure and other components of the metabolic syndrome (waist circumference and glucose levels). Similarly, in population-based cohorts, anti-inflammatory dietary patterns have also demonstrated associations with common carotid IMT and adiposity, but not with blood pressure.[42]

Most studies that examine associations of dietary inflammation with PWV or carotid IMT in adults tend to focus on high risk populations without considering community and/or population samples. This makes direct comparison with our results challenging. For example, adherence to an anti-inflammatory diet (Mediterranean or Dietary Approaches to Stop Hypertension) in both randomised and non-randomised controlled trials has been shown to improve carotid IMT, PWV and BP among clinical samples of adults with a high risk cardiovascular disease,[43-45] but whether these associations hold in population-based samples is unclear.

There are no comparable population-based data for children. One small community-based study demonstrated that although children's higher DII scores were associated with higher waist-to-height-ratio, there were no associations with blood pressure or heart rate.[14] Previous studies in childhood have focused on adherence to anti-inflammatory diets – neglecting possible contributions from pro-inflammatory foods – in participants with increased cardiovascular risk. In a small uncontrolled 12-month trial (n = 36) of pre-pubescent children with hypercholesterolaemia, carotid IMT fell with a Mediterranean diet intervention.[46]

However, in 237 children with a recent diagnosis of type I diabetes, a dietary pattern characterised by pro-inflammatory foods was not associated with higher PWV.[47]

Implications

Diet is one of the cornerstone lifestyle behaviours that can modulate the inflammatory process. The lack of associations of either inflammatory score with children's vascular phenotypes suggest that the negative effects associated with an inflammatory diet are cumulative and manifest only later in the lifecourse. In keeping with this cumulative lifecourse hypothesis, we showed associations of two inflammatory diet scores with vascular function and retinal arteriolar calibre in mid-life adults (the children's parents). However, the magnitude of associations was small and attenuated following adjustment for BMI, suggesting that the association of pro-inflammatory diets with cardiovascular health in mid-life adults may be mediated in part via BMI – itself an inflammatory condition. Nevertheless, although the magnitude of these results seems unlikely to be immediately clinically relevant, these small gradients within the normal range may be of importance to population health.

Further, if an inflammatory diet has small detrimental effects on vascular phenotypes in a healthy population-based mid-life cohort, more marked adverse changes seem likely with age due to ongoing cumulative exposure and other risk factors. Concerning the clinical and public health implications the present data suggest that among adults the dietary inflammatory pattern may provide useful information for preventive work. However, further research, especially longitudinal studies and intervention settings, is needed to replicate and confirm our findings.

Limitations

We recognise some limitations of this study. Our participants were, on average, slightly more advantaged socioeconomically and homogeneous than the general Australian population,

1 which may limit the generalisability to very disadvantaged people. Secondly, only 12% of the

2 adults were male. Thirdly, in comparison to the comprehensive and well-validated DII or a

3 nutrient intake survey, the NaSSDA's brevity means that our dietary scores do not capture all

4 dietary components (e.g. salt intake, alcohol and coffee) that may influence inflammation.

5 The beneficial trade-offs for such brevity are the large national cross-generational samples

6 and depth of cardiovascular measures. In addition, the self-reported nature of diet data may

7 be subject to inaccuracies and recall biases, particularly in children.[48, 49] Nonetheless,

8 previous studies have shown the fruit and vegetable items of the NaSSDA demonstrate good

9 validity when compared to adult reported 24-hour recall.[19] Fourthly, although the GlycA-

10 derived score used a new novel biomarker of inflammation, the child GlycA-derived score

11 was calculated using the coefficients from the adult GlycA analysis, as there are virtually no

12 data on GlycA in children. Diet and other factors may affect GlycA differently – and in as yet

13 unknown ways – at younger ages. Fifthly, given that we used an inflammatory biomarker to

14 derive one of the inflammatory diet scores, it is possible that we also captured any direct

15 association between inflammation (i.e. GlycA) and preclinical cardiovascular phenotypes.

16 However, the highly consistent results for the literature-derived score suggests we have

17 identified associations related to inflammatory diet and provides confidence in our results and

18 interpretation. Lastly, due to the cross-sectional nature of the study, temporal or causal

19 relationships cannot be addressed.

20

21 **Strengths**

22 Strengths include the large population-derived samples spanning a large geographical area,

23 the inclusion of individuals at two important life stages (late childhood and mid-life), and the

24 breadth and depth of objective measurements of preclinical cardiovascular phenotypes – both

25 structural and functional. All measurements were obtained using trained technicians and

qualified graders. The NaSSDA questionnaire, although brief, better reflects habitual dietary habits than food diaries or diet recalls.[50] Finally, the direction of our obtained effects is in the expected direction and is reinforced by replication between two related, but unique, inflammatory diet scores.

Conclusions

A pro-inflammatory diet was consistently associated with small adverse variations in preclinical cardiovascular phenotypes of function and microvascular structure in mid-life adults, but not in 11 to 12 year-olds. These findings support a lifecourse paradigm, where negative impacts of a pro-inflammatory diet on preclinical cardiovascular phenotypes may slowly accumulate to be detectable by mid-life, and presumably continue to accrue thereafter.

Conflict of interest

Financial support

1 **Author Contributions**

2 Dr Davis initiated this work as part of his student project, made substantial contributions to the
3 conception and design of the study, conducted the analyses, interpreted the data, drafted the
4 article, and revised it critically based on co-author feedback.

5 Dr Liu contributed to the study design, analysis of the data, interpretation of data, and revised
6 the article critically for important intellectual content.

7 Dr Kerr co-supervised Dr Davis, made substantial contributions to the conception and design
8 of the study, analysis of the data, interpretation of data, and revised the article critically for
9 important intellectual content.

10 Professor Wake is the Chief Investigator of The Child Health CheckPoint study, she
11 contributed to the study design, interpretation of data, and revised the article critically for
12 important intellectual content.

13 Dr Grobler contributed to the study design, provided statistical advice, interpretation of data,
14 and revised the article critically for important intellectual content.

15 Professors Juonala and Baur are Investigators on the Child Health CheckPoint study, they
16 made contributions to the study design, interpretation of data, and revised the article critically
17 for important intellectual content

18 Ms Liu contributed to the study design, interpretation of data, and revised the article critically
19 for important intellectual content.

20 Professor Burgner primary supervised Dr Davis and is an Investigator of The Child Health
21 CheckPoint study. He made substantial contributions to the conception and design of the study,
22 interpretation of data, and revised the article critically for important intellectual content.

23 Dr Lycett co-supervised Dr Davis, made substantial contributions to the conception and
24 design of the study, analysis of the data, interpretation of data, revised the article critically for
25 important intellectual content.

26 All authors approved the final manuscript as submitted and agree to be accountable for all
27 aspects of the work.

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Table 1. NaSSDA food items[a] and generation of both literature-derived and GlycA-derived scoring systems (Exposures)

Category (Frequency)	Question	Adult literature-derived score frequency			Adult GlycA-derived scores for each category		
		Assigned frequency	Child Mean (SD)	Adults Mean (SD)	Univariable p	Model 1 β; p	Model 2 β; p
Fish (Weekly)	How often do you eat fish, including canned fish?	**0:** 0 or 0.5 times **-1:** 1.5 or 3.5 times **-2:** 5.5 or 7 times	-0.4 (0.5)	-0.6 (0.5)	<0.001	-0.0142; <0.001	-0.0131; <0.001
Vegetables (Daily)	How many serves of vegetables do you usually eat each day?	**0:** 0, 0.5 or 1 serves **-1:** 2 or 3 serves **-2:** 4, 5 or 6 serves	-0.9 (0.7)	-1.1 (0.6)	<0.001	-0.0121; <0.001	-0.0133; <0.001
Fruit (Daily)	How many serves of fruit do you usually eat each day?	**0:** 0, 0.5 or 1 serves **-1:** 2 or 3 serves **-2:** 4, 5 or 6 serves	-1.0 (0.7)	-0.5 (0.6)	<0.001	-0.0027; 0.54	n/a
Chicken (Weekly)	How often do you eat chicken?	**0:** 0, 0.5, 1.5, 3.5 times **+1:** 5.5 or 7 times	0.0 (0.2)	0.0 (0.2)	0.06	0.0046; 0.13	0.0045; 0.14
Red meat (Weekly)	How often do you eat red meat?	**0:** 0 or 0.5 times **+1:** 1.5 or 3.5 times **+2:** 5.5 or 7 times	0.9 (0.5)	1.0 (0.4)	0.11	0.0004; 0.12	0.0045; 0.09
Meat products (Weekly)	How often do you eat meat products?	**0:** 0 or 0.5 times **+1:** 1.5 times **+2:** 3.5, 5.5 or 7 times	1.3 (0.7)	0.7 (0.7)	0.001	0.0018; 0.58	n/a
Bread (Daily)	How many slices of bread do you usually eat each day?	**0:** 0, 0.5, 1 or 2 slices day **+1:** 3 or 4 slices day **+2:** 6 or 8 slices day	0.4 (0.6)	0.1 (0.4)	<0.001	0.0015; <0.001	0.0016; <0.001
Milk (Daily)	How much milk in total do you usually drink each day?	**0:** 0, 0.5, 1 or 2 cups **+1:** 3 or 4 cups **+2:** 5 cups	0.2 (0.5)	0.1 (0.2)	0.18	0.0046; 0.38	n/a
Cheese (Weekly)	How often do you eat cheese?	**0:** 0, 0.5, 1.5, 3.5 or 5.5 times **+1:** 7 times	0.1 (0.3)	0.1 (0.3)	0.003	-0.0053; 0.02	-0.0049; 0.021
Milk products (Weekly)	How often do you eat milk products such as yoghurt, chocolate milk, pudding etc.?	**0:** 0, 0.5, 1.5, 3.5 or 5.5 times **+1:** 7 times	0.1 (0.3)	0.1 (0.3)	<0.001	-0.0041; 0.05	-0.0037; 0.07

Category (Frequency)	Question	Adult literature-derived score frequency			Adult GlycA-derived scores for each category		
		Assigned frequency	Child Mean (SD)	Adults Mean (SD)	Univariable p	Model 1 β; p	Model 2 β; p
Fruit juice (Weekly)	How much fruit juice do you usually drink?	**0:** 0, 0.5, 2 times **+1:** 5 times **+2:** 10.5, 24.5 or 35 times	0.2 (0.6)	0.1 (0.4)	<0.001	0.0060; 0.004	0.0059; 0.01
Water (Daily)	How much water do you usually drink each day?	**0:** regardless of consumption	0.0 (0.0)	0.0 (0.0)	0.18	0.0042; 0.18	0.0040; 0.20
Sugar drinks (Weekly)	How much soft drinks, cordials or sports drinks do you usually drink?	**0:** 0 or 0.5 cups **+1:** 2 or 5 cups **+2:** 10.5, 24.5 or 35 cups	0.4 (0.6)	0.2 (0.5)	<0.001	0.0018; 0.11	0.0020; 0.08
Energy drinks (Weekly)	How much energy drinks do you usually drink?	**0:** 0 or 0.5 cups **+1:** 2 or 5 cups **+2:** 10.5, 24.5 or 35 cups	0.0 (0.2)	0.0 (0.2)	<0.001	0.0026; 0.67	n/a
Pastas (Weekly)	How often do you eat pasta, rice or noodles?	**0:** 0, 0.5, 2, 5 or 7 times **+1:** 14 times	0.0 (0.1)	0.0 (0.1)	0.46	n/a	n/a
Ice confection (Weekly)	How often do you have ice cream, icy poles or ice blocks?	**0:** 0, 0.5 or 1.5 times **+1:** 3.5 or 5.5 times **+2:** 7 times	0.3 (0.5)	0.1 (0.3)	0.01	0.0047; 0.25	n/a
Fried potato (Weekly)	How often do you eat hot chips, french fries, wedges or fried potatoes?	**0:** 0, 0.5 or 1.5 times **+1:** 3.5 times **+2:** 5.5 or 7 times	0.1 (0.3)	0.0 (0.2)	<0.001	0.0118; 0.09	0.0140; 0.05
Chips/crisps (Weekly)	How often do you eat potato crisps/chips or other salty snacks?	**0:** 0, 0.5 or 1.5 times **+1:** 3.5 times **+2:** 5.5 or 7 times	0.3 (0.6)	0.1 (0.3)	0.003	-0.0023; 0.60	n/a
Takeaway (Weekly)	How often do you have meals or snacks such as burgers, pizza, chicken or chips?	**0:** 0 or 0.5 times **+1:** 1.5 times **+2:** 3.5, 5.5 or 7 times	0.4 (0.6)	0.2 (0.4)	<0.001	0.0395; <0.001	0.0396; <0.001
Confectionery (Weekly)	How often do you eat confectionery?	**0:** 0, 0.5, 1.5, 3.5 or 5.5 times **+1:** 7 times	0.0 (0.1)	0.0 (0.2)	0.02	-0.0057; 0.02	-0.0056; 0.02
Sweet foods (Weekly)	How often do you eat sweet foods, such as sweet biscuits, cakes or muffins?	**0:** 0, 0.5, 1.5 or 3.5 times **+1:** 5.5 times **+2:** 7 times	0.1 (0.4)	0.1 (0.4)	0.002	-0.0090; <0.001	-0.0086; 0001

[a] Table excludes 3 food items that examined breakfast, cereals and diet-drinks as their inflammatory value was deemed unclear

1 Table 2. Child regression coefficients estimating variation in preclinical CV phenotypes for each SD unit higher in inflammatory diet scores

11-12 year-olds CV intermediate phenotypes	Mean (SD)	Adjusted for age, sex, SEP and puberty		Additionally adjusted for BMI z-score	
		β (95% CI)	p	β (95% CI)	p
Literature-derived inflammatory diet score (SD units)					
Carotid intima-media thickness max (µm)	581 (46)	-0.4 (-2.9 to 2.1)	0.76	[a]-0.3 (-2.8 to 2.3)	0.84
Retinal arteriolar calibre (µm)	159.0 (11.9)	0.34 (-0.35 to 1.03)	0.33	0.26 (-0.42 to 0.94)	0.45
Retinal venular calibre (µm)	230.5 (16.5)	0.21 (-0.75 to 1.17)	0.67	0.22 (-0.74 to 1.18)	0.65
Pulse wave velocity (m/s)	4.46 (0.57)	-0.01 (-0.04 to 0.02)	0.35	-0.01 (-0.03 to 0.02)	0.64
Systolic blood pressure (mmHg)	108.2 (7.9)	-0.4 (-0.8 to 0.0)	0.07	-0.1 (-0.5 to 0.3)	0.51
Diastolic blood pressure (mmHg)	62.4 (5.7)	-0.1 (-0.3 to 0.3)	0.76	0.02 (-0.3 to 0.3)	0.90
Mean arterial pressure (mmHg)	76.1 (6.3)	-0.2 (-0.5 to 0.2)	0.38	-0.02 (-0.3 to 0.3)	0.90
GlycA-derived inflammatory diet score (SD units)					
Carotid intima-media thickness max (µm)	As above	0.9 (-1.6 to 3.4)	0.48	[c]0.8 (-1.7 to 3.3)	0.53
Retinal arteriolar calibre (µm)		0.42 (-0.27 to 1.11)	0.23	0.44 (-0.24 to 1.12)	0.21
Retinal venular calibre (µm)		-0.29 (-0.99 to 0.93)	0.95	-0.03 (-0.99 to 0.93)	0.95
Pulse wave velocity (m/s)		-0.00 (-0.03 to 0.03)	0.95	-0.00 (-0.03 to 0.02)	0.82
Systolic blood pressure (mmHg)		-0.1 (-0.5 to 0.4)	0.80	-0.1 (-0.4 to 0.3)	0.78
Diastolic blood pressure (mmHg)		0.0 (-0.3 to 0.3)	0.94	0.0 (-0.3 to 0.3)	0.94
Mean arterial pressure (mmHg)		0.0 (-0.3 to 0.4)	0.80	0.0 (-0.3 to 0.4)	0.79

~~Adjusted for age, sex, socioeconomic position and pubertal status;~~ [b]~~Additionally adjusted for BMI z-score~~; [ca]Further adjusted for minimal vessel diameter.

CV: cardiovascular; β: Estimated regression coefficient, SEP: socioeconomic position; BMI: Body Mss Index; CI: confidence interval; SD: standard deviation, µm: micrometres, m/s: metres per second, mmHg: millimetres of mercury

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Table 3. Adult regression coefficients estimating variation in preclinical CV phenotypes for each SD unit higher in inflammatory diet scores

Adults (mean age: 44 yrs) CV intermediate phenotypes	Mean (SD)	Adjusted for age, sex, SEP		Additionally adjusted for BMI	
		β (95% CI)	p	β (95% CI)	p
Literature-derived inflammatory diet score (SD units)					
Carotid intima-media thickness max (µm)	663.0 (97.2)	-0.3 (-5.2 to 4.6)	0.91	-3.5 (-8.4 to 1.4)	0.16
Retinal arteriolar calibre (µm)	151.24 (13.86)	-1.20 (-2.01 to -0.39)	0.004	-0.80 (-1.62 to 0.02)	0.06
Retinal venular calibre (µm)	219.03 (18.52)	-0.01 (-1.10 to 1.07)	0.98	-0.03 (-1.1 to 1.1)	0.96
Pulse wave velocity (m/s)	6.86 (1.13)	0.09 (0.04 to 0.15)	0.001	0.03 (-0.02 to 0.09)	0.21
Systolic blood pressure (mmHg)	119.4 (12.6)	0.6 (-0.1 to 1.2)	0.08	-0.3 (-0.8 to 0.3)	0.34
Diastolic blood pressure (mmHg)	73.0 (8.6)	0.5 (0.1 to 1.0)	0.02	0.2 (-0.3 to 0.6)	0.48
Mean arterial pressure (mmHg)	86.5 (10.2)	0.7 (0.2 to 1.2)	0.01	0.0 (-0.4 to 0.6)	0.71
GlycA-derived inflammatory diet score (SD units)					
Carotid intima-media thickness max (µm)	As above	0.1 (-4.8 to 5.0)	0.97	-5.1 (-10.0 to -0.1)	0.04
Retinal arteriolar calibre (µm)		-1.29 (-2.10 to -0.49)	0.002	-0.70 (-1.53 to 0.14)	0.10
Retinal venular calibre (µm)		0.62 (-0.46 to 1.70)	0.26	0.64 (-0.49 to 1.77)	0.27
Pulse wave velocity (m/s)		0.17 (0.11 to 0.22)	<0.001	0.07 (0.02 to 0.12)	0.01
Systolic blood pressure (mmHg)		1.7 (1.0 to 2.3)	<0.001	0.3 (-0.3 to 0.8)	0.39
Diastolic blood pressure (mmHg)		1.4 (0.9 to 1.8)	<0.001	0.7 (0.3 to 1.2)	0.001
Mean arterial pressure (mmHg)		1.9 (1.3 to 2.4)	<0.001	0.9 (0.4 to 1.4)	<0.001

β: Estimated regression coefficient, CI: confidence interval; SEP: socioeconomic position; BMI: Body Mss Index; SD: standard deviation, µm: micrometres, m/s: metres per second, mmHg: millimetres of mercury, yrs: years, CV: cardiovascular.

3

Supp Table 1. Sample characteristics

Characteristics	Children [a]Mean (SD)	Adults [a]Mean (SD)
Demographics	[b](n=1,771)	[b] (n=1,793)
Age (years)	11.5 (0.5)	43.7 (5.2)
Male, %	50.6	12.3
BMI z-score	0.3 (1.0)	-
BMI (kg/m^2)	-	27.8 (6.1)
Overweight, %		
Obese, %		
Socioeconomic position z-score	0.2 (1.0)	0.2 (1.0)
Puberty, %		
Early/Mid-pubertal	76.77	-
Smoked in the preceding 10 years, %	-	16
Ever exposed to passive smoke in the household, %	15	
Reported previous CV condition, %	-	8
Reported diabetes mellitus, %	0.3	1.5
Inflammatory diet scores		
Literature-derived	2.50 (3.04)	0.77 (2.46)
Data-derived	0.06 (0.06)	0.03 (0.06)
Intermediate CV phenotypes		
Vascular structure		
Carotid intima-media thickness mean (µm)	497.3 (58.9)	568.4 (76.1)
Retinal arteriolar calibre (µm)	159.01 (11.89)	151.24 (13.86)
Retinal venular calibre (µm)	230.54 (16.48)	219.03 (18.52)
Vascular function		
Pulse wave velocity (m/s)	4.46 (0.57)	6.86 (1.13)
Systolic blood pressure (mmHg)	108.16 (7.94)	119.39 (12.59)
Diastolic blood pressure (mmHg)	62.39 (5.74)	73.04 (8.58)
Mean arterial pressure (mmHg)	76.12 (6.34)	86.45 (10.19)

[a]unless otherwise specified;

[b]N's ranged from 1,771-1,657 for children and 1,793-1,623 for adults. The exceptions were carotid intima-media thickness, which was collected at Main and Mini Assessment Centres (1,407 for children and 1,431 for adults), and retinal vessel calibre, which was only collected at Main Assessment Centres (1,222 for children and 1,234 for adults).

[c]Adults self-reported either having a heart condition, high blood pressure or taking high cholesterol or blood pressure medication.

BMI: Body Mass Index, SD: standard deviation, µm: micrometres, cm: centimetres, m/s: metres per second, kg: kilograms, mmHg: millimetres of mercury.