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# Dietary patterns derived by reduced rank regression and non-communicable disease risk

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Most current nutrition policies and dietary recommendations still reflect decades of research addressing the mechanism of action or health risks of individual nutrients. Yet, most high-income countries including the UK are far from reaching the dietary intakes which are recommended for good health. Food-based dietary patterns (DPs) can help target specific combinations of foods that are associated with disease risk, recognising the coexistence of multiple nutrients within foods and their potential synergistic effects. Reduced rank regression (RRR) has emerged as a useful exploratory approach which uses *a priori* knowledge of the pathway from diet to disease to help identify DPs which are associated with disease risk in a particular population. Here we reviewed the literature with a focus on longitudinal cohort studies using RRR to derive DPs and reporting associations with non-communicable disease risk. We also illustrated the application of the RRR approach using data from the UK Biobank study, where we derived DPs that explained high variability in a set of nutrient response variables. The main DP was characterised by high intakes of chocolate and confectionery, butter and low-fibre bread, and low intakes of fresh fruit and vegetables and showed particularly strong associations with CVD, type 2 diabetes and all-cause mortality, which is consistent with previous studies that derived ‘Western’ or unhealthy DPs. These recent studies conducted in the UK Biobank population together with evidence from previous cohort studies contribute to the emerging evidence base to underpin food-based dietary advice for non-communicable disease prevention.

**Key words:** Dietary patterns: Reduced rank regression: CVD: Diabetes

The burden of non-communicable diseases such as heart disease or diabetes continues to increase, and this trend is accelerated by poor dietary habits<sup>(1–3)</sup>. Many of the top twenty risk factors reported in the Global Burden of Disease study are related to diet, including low intakes of whole grains, legumes, nuts, fruits, fibre or vegetables, and high intakes of red and processed meats, *trans* fat or sodium<sup>(4)</sup>. Despite efforts to improve population diets, most high-income countries including the UK are far from reaching recommended dietary intakes consistent with good health<sup>(5)</sup>. Many current policies and dietary

recommendations are still based on single nutrients or foods<sup>(6,7)</sup>, and media attention often focuses on one specific nutrient (e.g. sugar or saturated fat). In reality, food intake is a multi-dimensional exposure with many dietary risk factors showing high correlations between themselves, and the biological effects of different nutrients may also have synergistic effects<sup>(8,9)</sup>.

A whole-diet approach to disease prevention is increasingly being adopted in policy and practice. There are several methods to derive dietary patterns (DPs) but this review focuses on reduced rank regression

**Abbreviations:** DP, dietary pattern; RRR, reduced rank regression; SSB, sugar-sweetened beverage.

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(RRR), which uses *a priori* knowledge about risk factors or nutrients of concern to help identify DPs in a particular study population<sup>(10)</sup>. We include a detailed explanation of the RRR approach to derive DPs from the research by the authors in the UK Biobank study. The UK Biobank study is a prospective cohort that recruited over 500 000 adults, aged 40–69 at baseline (2006–2010), who provided detailed measures of dietary intake. Together with previous evidence from longitudinal cohort studies using RRR-derived DPs, we present observational associations between RRR-derived DPs and the risk of health outcomes as well as other cardiometabolic risk factors in the UK Biobank population<sup>(11,12)</sup>.

### Dietary pattern research

A whole-diet approach is an important tool in nutrition research to capture the inherently complex nature of food intake. Energy intake in human subjects has been shown to be relatively stable, and this implies that changes in one food or nutrient will be associated with changes in another one, also known as substitution effects<sup>(13,14)</sup>. Therefore, making inferences about a particular food or nutrient in observational studies is problematic and residual confounding will likely affect the observed associations with health outcomes. DP approaches can potentially overcome these issues, while capturing any synergistic effects and the cumulative exposure to different foods and nutrients<sup>(9)</sup>, which in turn may result in stronger associations with health outcomes than what has been observed with single nutrients or foods<sup>(8,10)</sup>.

In observational studies, there are two main approaches used to derive DPs using self-reported measures of dietary intakes: *a priori* or pre-defined DP, and *a posteriori* or data-driven/exploratory DP<sup>(8,15)</sup>. Pre-defined DP approaches include specific diets (i.e. vegetarian or vegan) as well as dietary indices or scores, which are used as a proxy for adherence to a particular diet (i.e. Mediterranean dietary score, healthy eating index). Exploratory approaches are data-driven because they use different statistical techniques to derive particular combinations of food groups from dietary data collected in a specific population. The most widely used exploratory approaches include factor and principal component analysis, partial least squares and RRR.

Both *a priori* and *a posteriori* approaches aim to reduce a large amount of information from complex diets in order to investigate diet–disease associations, but all these methods have particular pros and cons that have been summarised elsewhere<sup>(8,9,15)</sup>. In any case, it is critical to choose the most appropriate approach that aligns with a well-developed research question, as this can influence the observed associations with disease risk<sup>(8,10,16)</sup>.

### Dietary patterns derived by reduced rank regression

RRR has emerged as a useful hybrid approach which uses *a priori* knowledge about nutrients or biomarkers with an established link with disease, to help identify data-driven combinations of foods in a particular

population<sup>(10)</sup>. In common with all the other exploratory approaches, the RRR method aims to extract successive linear combinations of predictor variables (i.e. food groups). However, the main goal of RRR is to explain the maximum variability in response variables (i.e. nutrients of interest with established associations with disease risk); while the other exploratory approaches aim to maximise the variability in the predictors (principal component analysis) or a balance between predictor and response variation (partial least squares)<sup>(10)</sup>.

The RRR model can include one or more response variables, and a number of uncorrelated factors (DPs) will be derived which is equal to the number of specified response variables in the model. The variation in each of the response variables that is explained by each DP gives an indication of the likely ‘strength’ between each DP and each response variable. Typically, the DPs that explain the maximum variability in all the response variables collectively are retained for analysis. Each predictor variable in the model (i.e. food group) will also receive a factor loading, so that a larger value (positive or negative) indicates that the food group makes a greater contribution to the DP. Participants in a study population can then obtain an overall score (*z* score) for each of the derived DPs based on the factor loading and their intake of each food group, representing the degree to which their dietary intake adheres to a DP relative to other participants.

A key strength of the RRR approach is that the derived DPs use *a priori* knowledge of established associations between biomarkers or nutrients of interest and disease, hence it is particularly appealing if the aim is to identify DPs in association with disease endpoints. The emerging DPs are food-based, meaning they are easier to interpret and communicate, which helps inform public health advice. However, RRR-derived DPs share limitations in common with the rest of approaches, for example, subjective decisions are made about the number of DPs that will be retained for analysis, and it is unclear which food group(s) may drive the associations. In particular, RRR relies on the availability of response variables with solid evidence of their associations with disease outcomes; and by choosing a specific set of nutrient response variables, there will be some variability explained by other nutrients which may also be involved in the disease pathway of interest<sup>(10,15)</sup>.

### Dietary patterns emerging from longitudinal cohort studies

The state of the evidence with regards to RRR-derived DPs and non-communicable diseases such as CVD and diabetes is gradually growing. A literature search on PubMed and Embase up to May 2022 returned seventeen studies using data from longitudinal cohorts looking at prospective associations between RRR-derived DPs with CVD risk and/or all-cause mortality<sup>(11,16–31)</sup>, and nineteen studies investigating associations with the risk of developing diabetes<sup>(12,32–49)</sup>. The vast majority of these studies have been published since 2015, and

have included samples from a variety of populations including the USA ( $n$  8<sup>(20,24,25,31,39,40,42,45,46)</sup>); Europe ( $n$  11<sup>(16,18,19,21,23,26,29,35–37,47,48)</sup>), Asia ( $n$  6<sup>(22,27,28,32,33,41,49)</sup>), UK ( $n$  4<sup>(11,12,30,34,43,44)</sup>) or others ( $n$  2<sup>(17,38)</sup>). Population specificity is important here, because even when the choice of response variables (e.g. nutrients) is the same, the emerging DPs can vary substantially between different populations, owing to cultural differences in food intakes.

Until very recently, evidence with regards to RRR-derived DPs in association with CVD and all-cause mortality risk in the UK population was limited to one small study<sup>(30)</sup>, while the evidence with regards to diabetes was constrained to two small cohort studies<sup>(43,44)</sup>. Here we focus on the use of the UK Biobank study to illustrate the application of the RRR approach to derive DPs and summarise the prospective associations between RRR-derived DPs and CVD<sup>(11)</sup>, type 2 diabetes<sup>(12)</sup> and all-cause mortality<sup>(11)</sup> in the context of previously conducted studies. We have also investigated associations with cardiometabolic risk factors (e.g. BMI, blood pressure or lipid biomarkers) to help understand potentially underlying mechanisms. The UK Biobank is a prospective cohort that recruited over 500 000 adults between 2006 and 2010, aged 40–69 years at baseline. Together with important information on demographic, lifestyle factors, medical history, physical measures (height and weight) and blood and urine samples, detailed dietary intake measures were collected through an online questionnaire (Oxford WebQ) administered via email on up to five times during approximately 1.5–2 years<sup>(50,51)</sup>. The WebQ is a validated 24-h dietary assessment tool which collected quantitative information on two hundred and six widely consumed foods and thirty-two beverages<sup>(52–54)</sup>. We developed a food grouping system to group the number of reported foods and beverages into fifty major food groups before including them into the RRR model<sup>(55,56)</sup>, as this would also facilitate obtaining meaningful and relevant DPs. Four nutrient response variables were included: energy density (kJ/g), saturated fat (% total energy), free sugars (% total energy) and fibre density (g/MJ). These nutrient variables have established associations with the development of obesity, type 2 diabetes and CVD<sup>(57–66)</sup>, which underscores the importance of a well-supported hypothesis underlying the proposed research. From the initial baseline cohort, a subsample of participants that provided at least two 24-h questionnaires ( $n$  ~117 000<sup>(11)</sup>;  $n$  ~120 000<sup>(12)</sup>) and free of disease at baseline, were included and the mean dietary intake across multiple assessments was calculated to derive DPs.

With four response variables, the RRR model extracted four DPs together explaining a total of 77% of variability in the response variables. The top two DPs explaining 43% (DP1) and 20% (DP2) of variability were retained for analyses. DP1 showed high factor loadings for chocolate and confectionery, butter and other spreads, low-fibre bread, table sugars, grain-based desserts, sugar-sweetened beverages (SSBs) among others; and low factor loadings for fresh fruit, vegetables and high-fibre breakfast cereals. DP1 showed strong positive

correlations with energy density, free sugars and saturated fat, but negative correlations with fibre. Conversely, DP2 showed high factor loadings for SSBs, fruit juice, table sugars and preserves, chocolate confectionery; and low factor loadings for high-fat cheese, butter and other animal fat spreads. DP2 showed a strong positive correlation with free sugars, but a negative correlation with saturated fat, while energy density or fibre were not correlated<sup>(11,12)</sup>.

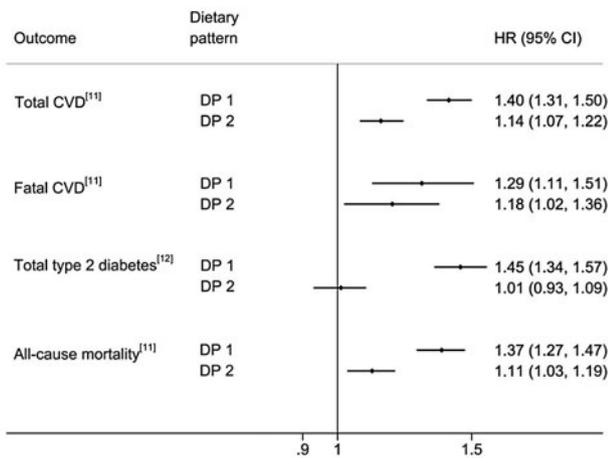
There is wide heterogeneity in previous studies regarding the choice of response variables in the RRR model, and most studies included combinations of nutrients<sup>(16,21,34,44,67)</sup> (% energy from monounsaturated fats and polyunsaturated fats; protein and total carbohydrates), as well as biomarkers<sup>(25,27,32)</sup> or disease risk factors (BMI, waist circumference, blood lipids or blood pressure)<sup>(30,35,38,49)</sup>. The majority of these previous studies obtained dietary measurements from food frequency questionnaires with fewer using either 24 h recalls or food records/diaries. The resulting DPs yielded combinations of food groups which were population-specific, although most studies identified at least one unhealthy or ‘Western’ DP characterised by high intakes of soft drinks, alcohol, refined carbohydrates, added sugars, fats, meat (including processed) and low fruit/vegetable intakes.

## Associations with health outcomes

### CVD

Previous research studies have derived CVD-related DPs and their associations with several outcomes, mostly using response variables such as CVD biomarkers or risk factors<sup>(18,20,26,29–31,35,68)</sup> as oppose to nutrients<sup>(11,16,21,25)</sup>. In common with the DPs derived in the UK Biobank population, most of these previous DPs were characterised by intakes of high-fat/high-sugar, refined carbohydrates (i.e. low-fibre bread, table sugars, SSBs) and high saturated fat foods (i.e. butter and animal spreads, red and processed meats), but low intakes of fruit, vegetables or higher-fibre foods. Of the studies performed in US cohorts, one reported significant associations between DPs characterised by high meat and refined carbohydrates/potato products but low fruit intakes with CVD mortality<sup>(20)</sup>; and another one reported a DP characterised by high intakes of fats, SSBs, meat, but low vegetables in association with a higher incidence of stroke<sup>(31)</sup>. In European populations, a study in Germany reported significant inverse associations with CVD mortality among those following a DP high in whole grain, fruits, cereals and vegetables but low intakes of processed meat, butter and cheese<sup>(29)</sup>. Another study among Swedish participants with obesity reported a significant association with total CVD in people following an energy-dense, high SFA, low-fibre DP<sup>(21)</sup>. A study in the UK Whitehall II study reported significant associations with incident CHD in association with a DP characterised by high intakes of white bread, fried potatoes, added sugars, processed meat and SSBs but low intakes of vegetables<sup>(30)</sup>.

The associations between DPs obtained in the UK Biobank population and several health outcomes are



**Fig. 1.** Risk of health outcomes associated with dietary pattern 1 (DP1) and dietary pattern 2 (DP2) in the UK Biobank study. Adjusted hazard ratios (HR) and 95 % CI, showing the risk of each DP for people in the fifth quintile (indicating the highest adherence to each DP). Estimates were obtained from Cox proportional hazard models using age during study as the underlying timescale. The models were stratified by sex and regions (England, Scotland and Wales) and adjusted for socio-demographic characteristics: ethnicity (white, others, missing), Townsend index of deprivation (quintiles one to five, with higher scores representing greater deprivation), education (higher degree [college or university degree, or professional qualifications], any school degree [A levels, AS levels, O levels, General Certificate of Secondary Educations or Certificate of Secondary Educations], vocational qualifications [National Vocational Qualifications, Higher National Diploma or Higher National Certificate], other [none of the above qualifications], missing); behavioural risk factors: smoking status (never, current, previous, missing), physical activity (low [ $<600$  metabolic equivalent (MET)-minutes per week], moderate [ $\geq 600$  and  $<3000$  metabolic equivalent (MET)-minutes per week], high [ $\geq 3000$  metabolic equivalent (MET)-minutes per week], missing), log-transformed energy intake; and health history/conditions: family history of diabetes, menopause in women, hypertension, CVD, high cholesterol.

summarised in Fig. 1<sup>(11)</sup>. People in the highest quintile of adherence to DP1 showed a 40 % higher risk of total cardiovascular events and 29 % higher risk of fatal CVD events compared to people in the first quintile. DP2 showed non-linear associations, although there were 14 % higher risk of total CVD and 18 % higher risk of fatal CVD among people in the highest quintile of DP2 compared to those in the lowest quintile. Adjustment for the BMI revealed slightly attenuated associations only for the associations observed with DP1, suggesting that the observed association was potentially mediated through excess weight. These observations are broadly consistent with previous evidence from single-nutrient studies or other DP studies using dietary quality scores<sup>(69–72)</sup>.

### Diabetes

Most previous studies have investigated associations between DPs and incident type 2 diabetes using response variables such as biomarkers<sup>(38,39,42,49)</sup>, diabetes markers such as HbA1c or the homeostasis model assessment of insulin resistance<sup>(32,37,41,43)</sup> or nutrients<sup>(12,34,44,67)</sup>. In the

US population, two studies found DPs characterised by high intakes of red meat/meat products, refined carbohydrates, SSBs that were significantly associated with type 2 diabetes<sup>(38,42)</sup>, while the opposite DP characterised by high intakes of whole grains, fruit, vegetables and low-fat dairy was inversely associated with type 2 diabetes<sup>(39)</sup>. A study among German adults reported a DP rich in fresh fruit but low in SSBs, alcohol, red/processed meat that was inversely associated with type 2 diabetes<sup>(37)</sup>; while less traditional DPs among Asian populations were generally associated with type 2 diabetes incidence<sup>(32,41,49)</sup>. Two small studies including UK middle-aged adults reported a high fat/glycaemic index DP<sup>(44)</sup> and a DP with high intakes of SSBs, fast foods/snacks, white bread<sup>(43)</sup> which were both significantly associated with type 2 diabetes. The associations observed in the UK Biobank study with type 2 diabetes showed that those in the highest quintile of adherence to DP1 showed a 45 % higher risk of incident diabetes compared to people in the first quintile (Fig. 1)<sup>(12)</sup>. However, there were non-significant associations between DP2 and diabetes incidence. Adjustment for BMI in the main model also attenuated the association observed with DP1, while the association with DP2 remained not statistically significant.

Most of the food groups and underlying nutrients that characterise DP1 in the UK Biobank study as well as other unhealthy DPs derived in previous cohorts have been shown to be significantly associated with diabetes and adverse metabolic effects<sup>(73,74)</sup>, particularly for chocolate confectionery<sup>(75)</sup>, SSBs<sup>(76,77)</sup> or added sugars<sup>(78)</sup>; as well as low consumption of fruits, vegetables and higher-fibre bread<sup>(79,80)</sup>. For the unexpected lack of association between DP2 and diabetes, it is important to note that this DP was characterised by high intakes of foods rich in free sugars but in the context of low intakes of saturated fat rich foods and energy density, and adequate intakes of fibre. This finding supports previous evidence suggesting that free sugars increase diabetes risk through increased energy intake and consequently weight gain, rather than through independent effects<sup>(64,81)</sup>. This has also been observed in short- and medium-term isoenergetic intervention trials showing no effects of free sugars on body weight or blood pressure<sup>(82)</sup>.

### All-cause mortality

The associations with CVD and diabetes observed in previous studies as well as the UK Biobank support the associations observed with the overall risk of mortality. Previous US and European cohort studies have generally reported significant associations between unhealthy/Western DPs and all-cause mortality<sup>(16,20,25,26)</sup>. In the UK Biobank<sup>(11)</sup>, people in the highest quintile of adherence to DP1 showed a 37 % higher risk of all-cause mortality compared to people in the first quintile (Fig. 1). DP2 showed somewhat weaker associations, with 11 % higher risk of all-cause mortality among people in the highest quintile compared to those in the lowest quintile. These associations generally mirror the ones observed with total and fatal CVD events, which supports the

evidence showing that CVD contributes a higher burden to total mortality than diabetes<sup>(83)</sup>.

For this particular outcome, diet is one of the multiple factors that may act synergistically with others (i.e. smoking, physical activity, socioeconomic status) which can influence mortality risk, hence the results observed with all-cause mortality have to be carefully interpreted given the possibility of residual confounding in these associations due to non-dietary differences between the groups.

#### *Cardiometabolic risk factors*

Several studies have reported associations between DPs and markers of cardiometabolic risk which collectively help understand potential underlying mechanisms in the observed associations with non-communicable disease risk. A US study showed that a DP characterised by high SSBs, meat, potatoes was associated with markers of arterial stiffness<sup>(68)</sup>; while other studies in Swedish adults showed a higher incidence of metabolic syndrome among people following a Western DP<sup>(35)</sup>; and positive associations with cardiometabolic risk factors among people with obesity and high adherence to an energy-dense high SFA low-fibre DP<sup>(21)</sup>. Cross-sectional analyses in the UK Biobank population showed significant associations between the DPs and several cardiometabolic risk factors measured at baseline<sup>(11)</sup>. For DP1, people adhering the most to this pattern showed particularly large differences in baseline BMI (BMI 27.1 kg/m<sup>2</sup> in the highest quintile compared to BMI 25.4 kg/m<sup>2</sup> in the lowest quintile), and somewhat smaller differences in diastolic blood pressure (82 mmHg in the highest quintile compared to 79.7 mmHg in the lowest quintile) and HDL cholesterol (1.41 mmol/l in the highest quintile compared to 1.59 mmol/l in the lowest quintile). For DP2, there were no clear associations with baseline markers, except for a small clinical difference in LDL cholesterol (3.62 mmol/l in the highest quintile compared to 3.70 mmol/l in the lowest quintile) and HDL (1.45 mmol/l in the highest quintile compared to 1.57 mmol/l in the lowest quintile).

#### **Strengths and limitations**

The evidence summarised here comes from longitudinal cohort studies, with wide variability in population characteristics and sample sizes. The UK Biobank is one of the largest contemporary cohorts of UK adults who provided detailed measures of dietary intake, which is essential to investigate the associations between food-based DPs and long-term disease risk. The follow-up times since completion of the dietary questionnaires (from 5–8 years) was sufficient to accumulate enough cases of CVD, diabetes and all-cause mortality and to achieve more precise estimates of association. Linkages with electronic health records also allowed for an objective ascertainment of cases.

However, previous research as well as recent studies by the authors in the UK Biobank share common

limitations that are inherent to observational studies. The derived DPs are based on self-reported measures of dietary intakes, which can be over- and/or underreported by participants introducing biases, although people with implausible dietary intakes were excluded in the studies by the authors. Day-to-day variation in diet was partly accounted for by including at least two dietary questionnaires, but some degree of bias due to random variation will remain<sup>(84)</sup>. In terms of investigating the associations between dietary exposures and longer-term health, it is clear that a lifetime exposure to a poor diet is a major determinant. However, most studies collected measurements of diet over a short time-period before disease manifestation and this may only reflect the most recent portion of this exposure. It is also unknown if DPs are stable over time or if changes preceding disease may affect the results. As with any observational research, caution is needed to avoid any causal inference and residual confounding (even after careful adjustment is made) cannot be ruled out. The cross-sectional associations investigating potential mechanisms through the associations with cardiometabolic risk factors measured at baseline may be affected by reversed causality, therefore careful interpretation is warranted. Finally, DPs identified in each study are culturally specific and relevant to each population, hence generalisability to other populations or countries is limited.

The main advantage of using RRR over other DP methods is that it allows an investigation of the cumulative effects of the whole diet, hence reducing confounding due to other dietary aspects, while also incorporating the mechanistic evidence through the integration of nutrient response variables<sup>(10)</sup>. The interpretation of the results is based on foods rather than nutrients, providing a more specific evidence base to inform the development of food-based dietary guidelines and making it easier to develop public health nutrition policies. However, the RRR method hinges on an imperfect evidence base to identify the underlying response variables and their association with disease endpoints. By focusing on a limited set of nutrients and foods which usually cannot explain 100% of the nutrient response variance, it is possible that the emerging DPs contain other important nutrients which are involved in the biological pathway to disease but cannot be specified. For most chronic diseases there might be complex interactions in different metabolic pathways linking diet and disease, which may not be captured in a single RRR model with a limited number of response variables.

#### **Implications and conclusions**

In the context of previous evidence, recent DP research by the authors in the UK Biobank study supports current dietary recommendations for good health which emphasise reductions in saturated fat and free sugars, and increases in vegetables, fruits or grains, among others<sup>(6,7)</sup>. But this new evidence is food-based, and points towards diets which are lower in chocolate and confectionery, butter, low-fibre bread, added sugars and SSBs, and

higher in fresh fruit and vegetables and whole grain foods to reduce the risk of CVD, diabetes and limit premature mortality. This should also help avoid confusing messages to the public regarding specific nutrients (e.g. saturated fat and sugars), recognising that foods are mixtures of nutrients and there might be synergistic effects between them. By identifying patterns in population-specific cohorts the hope is that food-based dietary advice may help accelerate behaviour change because it helps target specific foods and their combinations which are culturally relevant.

In conclusion, a whole-diet approach to disease prevention is attracting increasing interest from researchers, practitioners and policymakers. RRR is a particularly useful tool to derive population-specific food-based DPs using *a priori* knowledge about biomarkers or nutrients of concern which mediate the associations between the emerging DPs and disease outcomes and to help provide culturally relevant information to underpin behaviour change strategies to reduce non-communicable diseases.

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### Conflict of Interest

None.

### Authorship

The authors had sole responsibility for all aspects of preparation of the paper.

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