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Mente A, Dehghan M, Rangarajan S, O'Donnell M...Yusuf S. Diet, cardiovascular disease, and mortality in 80 countries. Eur Heart J. 2023 Jul 21;44(28):2560-2579.

What We Know, Think We Know, or Are Starting to Know

In the early 20th Century, atherosclerosis and resulting cardiovascular disease [CVD] was considered to primarily be a disease of ageing [(1)]. This view was challenged both during and immediately after the Second World War by two lines of evidence.

The first was the evidence of dramatic declines in CVD mortality during the war years, which demonstrated in principle that CVD was reversible [(2)]. The second was the emergence of the concept of risk factors with the U.S. Framingham Study, which identified factors related to incidence of heart attacks: male sex, elevated blood cholesterol and blood pressure, and cigarette smoking [(3)]. We have covered this history in this previous Research Lecture.

In this immediate post-War period, it appeared that CVD was primarily a condition of affluence, as mortality rates surged in prosperous industrialised countries relative to populations living under more subsistence, traditional lifestyles and diets [(4)]. However, leap forward to the present and any such discrepancy is no longer evident; low-middle income countries [LMIC] now exhibit the highest global burden of CVD [(5)].

Worryingly, while many Western high-income countries exhibited a declining burden of CVD, certain high-income countries [HIC] are seeing a reversing of their trends, e.g., population subgroups in the U.S. and Britain have been experiencing increasing burden of CVD over the decade up to 2019 [(5)].

These trends between income levels of countries reflect the prevalence of risk factors between countries [e.g., differences in smoking rates], and access to and quality of healthcare [e.g., better access with higher income, higher quality in more affluent countries] [(5)].

Within the global burden of CVD, dietary risks are ranked as the second biggest contributing risk factor [(5)]. However, the relationships between dietary risk factors and CVD may differ between populations, and the associations of specific foods may differ in diverse cultural diets [(6)]. The PURE Study is the largest epidemiological study of diet including both LMIC and HIC, and the most recent publication from this ongoing cohorts' study is our focus in this Deepdive.

The Study

The Prospective Urban Rural Epidemiology [PURE] study is an ongoing multi-country study of 168,067 participants from cohorts in 21 countries across five continents. The countries range in income strata, including 17 LMIC and four HIC* [see ***Appendix** at the end for further details].

For the present study, the researchers developed a diet pattern score* [see ***Geek Box**, below for further details] for the dietary patterns observed in the PURE cohorts, based on six food categories: fruits, vegetables, legumes, nuts, fish, and dairy.

Based on the median [average] value in the cohort, a score of 0 [“unhealthy”] or 1 [“healthy”] was assigned for participants either below or above the median intake of that food category, respectively. Thus, the PURE Healthy Diet Score ranged from 0 [“least healthy”] to 6 [“most healthy”]. Participants were divided into quintiles [fifths] of PURE Healthy Diet Scores, and the analysis compared the highest to lowest scores, and also the associations for each quintile increase in scores.

Additionally, the PURE Healthy Diet Score was calculated for participants from three ongoing prospective follow-ups of randomised controlled trials [RCTs] of participants with vascular disease, and for participants from two case-control studies of MI and stroke, respectively. The outcomes from the PURE cohort were compared against the associations of the PURE Healthy Diet Score and CVD outcomes in those studies. The outcomes for PURE and each of the five external validation cohorts were also combined in a meta-analysis.

The primary outcomes were major CVD, myocardial infarction [MI], and stroke, and a composite of total mortality and major CVD combined. Outcomes were reported as hazard ratios [HR] and 95% confidence intervals [CI].

*Geek Box: Dietary Pattern Scores

Most approaches to dietary assessment in nutritional epidemiology focus on foods and nutrients as the exposure of interest. However, there are several different methods of analysing total dietary patterns or characteristics of dietary patterns, known as a "diet quality index", or "scores". This involves creating a numeric scoring system to represent the quality of the overall dietary pattern based on specific levels of intake of different food groups, foods, and nutrients, in that dietary pattern.

There are many examples of diet quality indices, including the Healthy Eating Index and Alternate Healthy Eating Index, the Mediterranean Diet Score, the Dietary Approaches to Stop Hypertension [DASH] Diet Score, and Low-Carb Diet Score. They provide a means to quantitatively assess the healthfulness of a dietary pattern, given "quality" is an ambiguous term for research purposes. The overall scoring range may then be used as a numeric variable for a statistical analysis, i.e., by comparing levels of adherence quantified numerically as "low", "moderate", or "high" adherence to that dietary pattern.

There are several ways an index may assess diet quality. Basing the index on food groups and nutrient intakes is the most common, e.g., an index may have "low-fat dairy" as a food group, and then thresholds in grams per day upon which higher or lower scores are assigned. Alternatively, polyunsaturated fats [PUFA] may have a threshold in percentages, to which higher or lower scores are assigned based on PUFA intake as percentage of total energy intake. In contrast, dietary components associated with negative health outcomes, including sugar-sweetened beverages and fruit juices, red/processed meats, trans fats, and sodium have points scores inverse to consumption.

This allows for the overall healthfulness of an individual's diet pattern to be quantified in a single number, and the overall scores in a cohort can be divided into different levels and analysed in relation to disease outcomes.

Results: The final sample for the present study consisted of 147,642 participants from all 21 countries included in the PURE study. Average baseline age was ~50-years, ~58% of participants were female, and ~53% resided in urban areas. Average baseline BMI was 25.8kg/m^2. The average follow-up duration was 9.3-years, during which 8,201 CVD events and 10,076 total deaths occurred.

The average baseline PURE Healthy Diet Score was 2.95 [out of 6], with regional differences evident; average diet scores increased as country income increased. Regionally, the highest average PURE Healthy Diet Score and intakes in grams of each of the specific six food components were observed in North America and Europe, the Middle East, and South America, while the lowest were observed in South Asia, Southeast Asia, Africa, and China [see figure, below].

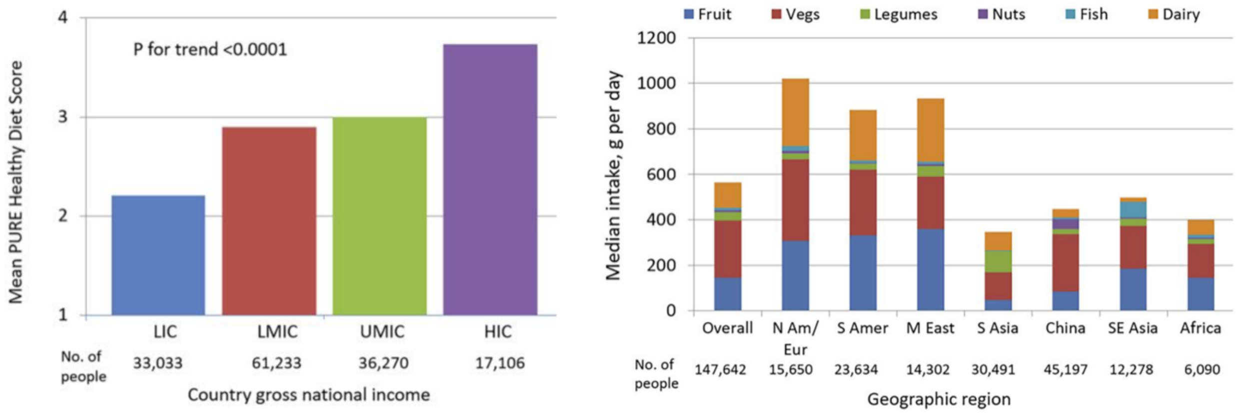


*Figure from the paper illustrating [**left**] the associations between country income level and average PURE Healthy Diet Score, and [**right**] the intakes of each of the six components of the score in grams per day in the overall cohort and in each of the regions of the included countries.*

The highest 20% of the PURE Healthy Diet Score [i.e., ≥5 points] correlated with the following intakes of the six specific components: 563g/d fruits and vegetables, 48g/d legumes, 28g/d nuts, 26g/d of fish, and 185g/d of dairy [of which 130g/d was whole-milk dairy]. Participants in this category averaged 54g/d red meat and 22g/d poultry. The macronutrient composition of this diet was 56% carbohydrate, 27% fat [of which 8.9% saturated and 15% unsaturated], and 17% protein.

Associations Between PURE Healthy Diet Score and CVD in PURE Cohort: Compared to the lowest diet scores, the highest were associated with the following outcomes:

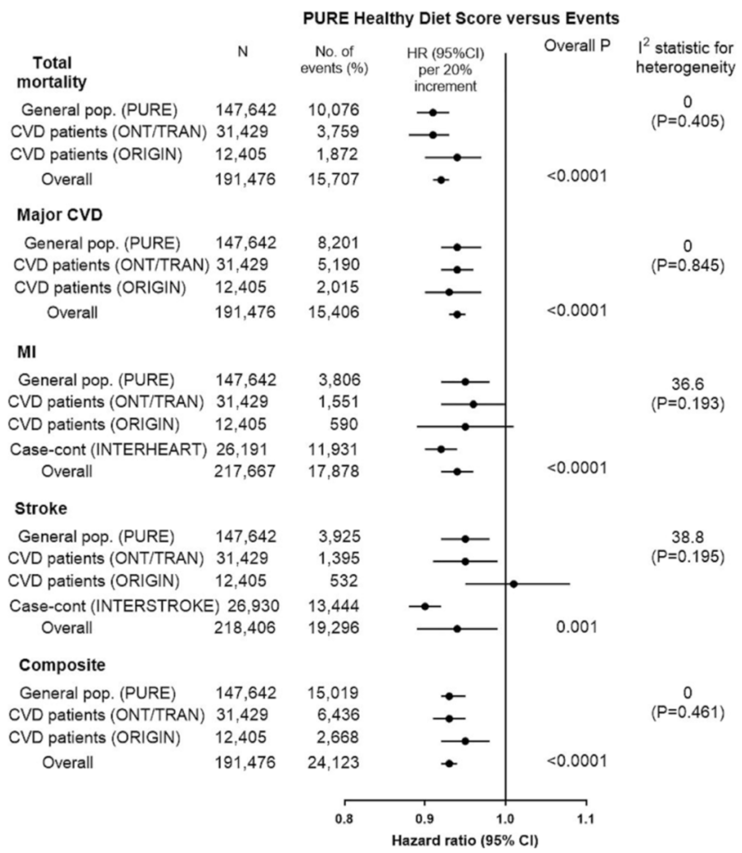
- **Major CVD**: 18% [95% CI, 9% to 25%] lower risk. Each 20% [i.e., quintile] increase in diet scores was associated with a 6% [95% CI, 3% to 8%] lower risk.
- **MI**: 14% [95% CI, 1% to 25%] lower risk. Each 20% [i.e., quintile] increase in diet scores was associated with a 5% [95% CI, 2% to 8%] lower risk.
- **Stroke**: 19% [95% CI, 7% to 29%] lower risk. Each 20% [i.e., quintile] increase in diet scores was associated with a 5% [95% CI, 2% to 8%] lower risk.
- **Total Mortality**: 30% [95% CI, 23% to 37%] lower risk. Each 20% [i.e., quintile] increase in diet scores was associated with a 9% [95% CI, 7% to 11%] lower risk.

Associations Between PURE Healthy Diet Score and CVD in Validation Cohorts: In the three included prospective RCT follow-ups, compared to the lowest diet scores the highest PURE Healthy Diet Scores were associated with similar strengths of associations as the primary analysis in the PURE cohort.

For example, major CVD was 20% [95% CI, 11% to 28%] lower in the combined analysis of the ONTARGET and TRASNCEND trials participants, and 23% [95% CI, 8% to 35%] lower in the analysis of the ORIGIN trial population.

In the analysis on MI with the population from the INTERHEART case-control study, the highest level of the PURE Healthy Diet Score was associated with a 28% [95% CI, 20% to 35%] lower risk. And in the analysis on stroke with the population from the INTERSTROKE case-control study, the highest level of the PURE Healthy Diet Score was associated with a 28% [95% CI, 20% to 35%] lower risk.

Meta-Analysis of All Included Cohorts: In the analysis combining participants from all four prospective cohorts, each 20% [quintile] increase in PURE Healthy Diet Scores was associated with an overall 6% lower risk of major CVD, MI, and stroke, respectively. Total mortality was 8% lower.



Forest plot from the paper illustrated the combined analysis included the PURE cohort, the three prospective follow-ups of RCTs [ONTARGET, TRANSCEND, and ORIGIN], and risk of the study outcomes. Each analysis for MI and STROKE also includes a case-control study, INTERHEART and INTERSTOKE, respectively.

The Critical Breakdown

Pros: The study aims were clearly stated. The follow-up duration was adequate, and the large number of events overall in a very large sample size provide strong statistical power to the study. The dietary analysis was based on country-specific validated food frequency questionnaires. The ORIGIN validation cohort also provided repeated assessment of diet in participants, which allowed for the present analysis to be adjusted for potential random measurement error. The use of several external validation cohorts, including three prospective and two case-control studies with large sample sizes, adds to the power of the present analysis [discussed further under ***Key Characteristic***, below]. The statistical analysis adjusted for relevant potential confounders, including the wealth index and urban vs. rural location.

Cons: The study did not define what "major CVD" was comprised of as an outcome in terms of specific CVD endpoints, which is an issue in observational research where different definitions may be applied [7]. The use of median levels of intakes within a food group to score healthfulness of diet may lack sensitivity to detect more precise thresholds of food intakes related to benefit. For example, the substantially stronger regional associations for regions with low average intakes of food groups may reflect a greater health gain relative to other regions [discussed further under ***Interesting Finding***, below]. The income strata of countries were based on 2006 World Bank data and may be outdated, e.g., Poland is classified as a middle-income country in PURE, but is now classified as a high-income country, while China is now classified as an upper middle-income country but is classified as a lower middle-income in PURE. The food component "dairy" was not well described [e.g., "milk", "yogurt", "yogurt drink"] which is a limitation given the importance of this food group to the overall Pure Healthy Diet Score and wider literature of nuanced differences in CVD risk related to specific dairy foods [as an example, see this previous Deepdive].

Key Characteristic

Diet pattern scores may exhibit degrees of specificity to a particular region or country, while also having broader application. However, with a diet score derived from a cohort like PURE, with 21 countries across five continents encompassing divergent socio-economic statuses and population characteristics, some caution would be required against the potential for ecological fallacy, i.e., extrapolating any associations from the PURE cohort alone to other specific or national contexts.

In this regard, an important strength of the present study is the application of the PURE Healthy Diet Score in five different validation cohorts. This concept of "validation" or "replication" cohorts is taken from genetic research, but is becoming more common in nutritional epidemiology [see this previous Deepdive and previous Research Lecture as examples of the application of this concept].

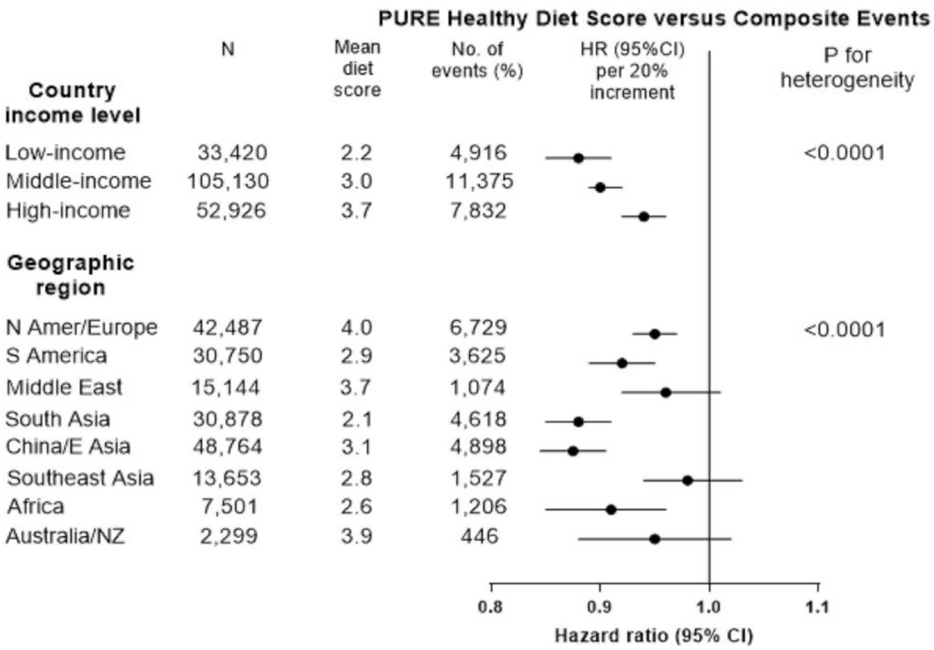
In the present study, the use of external cohorts allowed for the application of the PURE Healthy Diet Score in other cohorts, to test the strength of associations of the diet score beyond the characteristics of the PURE cohort alone. The three prospective RCT follow-ups totalled an additional 48,834 participants, while the case-control studies on MI and stroke totalled an additional 26,191 and 26,930 participants, respectively.

The validation cohorts were also multi-country studies, which adds to the validity of the replication of the findings from the analysis of the PURE cohort. The additional statistical power provided by the meta-analysis including the validation cohorts, and similar strengths of association, add confidence to the findings for the PURE Healthy Diet Score.

Interesting Finding

To build on the previous section, an example of why external validation is important is evident in the differing strengths of associations between country income strata and also region. The **figure** below from the paper illustrates this; we can clearly see that the greatest magnitude of risk reduction was evident in low-income countries, which also exhibited the lowest average PURE Healthy Diet Score.

This is also evident regionally [region and national income correlate], in which South Asia, China/East Asia, and Africa, exhibited the greatest magnitude of risk reduction by region in the context of low average PURE Healthy Diet Scores.



These findings are important because diets within a population and region tend to be more homogenous. Thus, conducting this subgroup analysis by region further reduces the possibility of ecological fallacy, as the direction of effect of the PURE Healthy Diet Score is consistent across regions, only the magnitude of the associations varies.

This highlights an important principle for interpreting nutrition research, which is that background dietary pattern and other population characteristics influence the strength of any associations between an exposure and outcome. It also highlights another important principle, which is that the greatest magnitude of benefit would be expected where an inadequate diet or insufficient nutrient intakes are increased into adequate/sufficiency ranges.

Relevance

Notwithstanding that the present study is an analysis based on a dietary pattern score, it is still important to consider population-level factors, and the specific food components of the dietary pattern.

In relation to the population-level factors, the analysis indicated that the lowest PURE Healthy Diet Scores correlated with the lowest estimated daily energy intakes, and intakes of each of the six food components of the diet score. This reflects the fact that the majority of data in PURE is derived from LMIC, and low energy and food intakes reflects nutritional inadequacy in these populations. Thus, consistent with the point made in the previous section, the greatest expected health gain and corresponding global CVD risk reduction would be expected in LMIC [5].

The second relates to specific food components. Ironically, the authors highlight the importance of "dose" in relation to the PURE Healthy Diet Score associated with greater risk reduction in populations with low average diet scores, but then ignore this principle when discussing red meat. In their analysis, including red meat in the diet score did not change the associations, i.e., still a lower CVD risk.

However, the average intake in the top 20% of diet scores was 54g/d, an intake typical of LMIC Asian and African countries, and within <100g/d levels that are not related to risk, as we covered in this previous Deepdive. The fact that they ignore the importance of "dose" here, but acknowledge it for the PURE Healthy Diet Score, indicates some spin on their results.

In relation to dairy, the authors also state that relative the Mediterranean or DASH diets, the PURE Healthy Diet Score is *"...a similar dietary pattern but which also includes dairy..."* This is a little bizarre given that dairy is a central component of the DASH diet, and also characteristic of the Mediterranean diet [8,9]. The authors doth protest too much, methinks.

Overall, the main relevance of the present study is how the global burden of CVD may be lowered through policies to improve nutritional adequacy in LMIC.

Application to Practice

In a previous Deepdive, we covered a study which examined the associations between international dietary guidelines and total and CVD mortality in a UK cohort, which highlighted the broad applicability of the main characteristics of a healthy dietary pattern.

While that analysis was based primarily on nutrient recommendations, the inherent flexibility of dietary pattern scores allows for similar characteristics to be identified in different population and regional contexts. For example, "fruits" as a category likely translates in food-based terms to different fruits in Spain compared to Thailand.

Thus, analyses like the present study are important additions to the literature because they demonstrate these similarities in cross-cultural contexts. Strip the present study back, and it is unsurprising that a dietary pattern high in the food components of the PURE Healthy Diet Score are associated with lower CVD risk.

Studies like this reassure us that there are many paths to a health-promoting diet, while reminding us that those with the most to gain from dietary improvements are often those in the least advantageous circumstances.

*Appendix: Countries of the PURE Study

The PURE Study classifies the income strata of countries based on the World Bank classification from 2006. Based on this classification, the countries in PURE includes five low-income countries [Bangladesh, India, Pakistan, Tanzania, and Zimbabwe], five lower middle-income countries [China, Colombia, Iran, Palestinian Territory (West Bank & Gaza), and the Philippines], seven upper middle-income countries [Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey], and four high-income countries [Canada, Saudi Arabia, Sweden, and United Arab Emirates]. PURE included 18 countries up to 2013, when three additional countries in the Philippines, Saudi Arabia, and Tanzania, were included by 2014, bringing the total number of countries included in the overall study to 21. Classification based on 2006 World Bank data may be outdated, as discussed under **Cons**, above.

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