Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study

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Summary

Background The association between intake of fruits, vegetables, and legumes with cardiovascular disease and deaths has been investigated extensively in Europe, the USA, Japan, and China, but little or no data are available from the Middle East, South America, Africa, or south Asia.

Methods We did a prospective cohort study (Prospective Urban Rural Epidemiology [PURE] in 135 335 individuals aged 35 to 70 years without cardiovascular disease from 613 communities in 18 low-income, middle-income, and high-income countries in seven geographical regions: North America and Europe, South America, the Middle East, south Asia, China, southeast Asia, and Africa. We documented their diet using country-specific food frequency questionnaires at baseline. Standardised questionnaires were used to collect information about demographic factors, socioeconomic status (education, income, and employment), lifestyle (smoking, physical activity, and alcohol intake), health history and medication use, and family history of cardiovascular disease. The follow-up period varied based on the date when recruitment began at each site or country. The main clinical outcomes were major cardiovascular disease (defined as death from cardiovascular causes and non-fatal myocardial infarction, stroke, and heart failure), fatal and non-fatal myocardial infarction, fatal and non-fatal strokes, cardiovascular mortality, non-cardiovascular mortality, and total mortality. Cox frailty models with random effects were used to assess associations between fruit, vegetable, and legume consumption with risk of cardiovascular disease events and mortality.

Findings Participants were enrolled into the study between Jan 1, 2003, and March 31, 2013. For the current analysis, we included all unrefuted outcome events in the PURE study database through March 31, 2017. Overall, combined mean fruit, vegetable and legume intake was 3·91 (SD 2·77) servings per day. During a median 7·4 years (5·5–9·3) of follow-up, 4784 major cardiovascular disease events, 1649 cardiovascular deaths, and 5796 total deaths were documented. Higher total fruit, vegetable, and legume intake was inversely associated with major cardiovascular disease, myocardial infarction, cardiovascular mortality, non-cardiovascular mortality, and total mortality in the models adjusted for age, sex, and centre (random effect). The estimates were substantially attenuated in the multivariable adjusted models for major cardiovascular disease (hazard ratio [HR] 0·90, 95% CI 0·74–1·10, p_{trend}=0·1301), myocardial infarction (0·99, 0·74–1·31; p_{trend}=0·2033), stroke (0·92, 0·67–1·25; p_{trend}=0·7092), cardiovascular mortality (0·73, 0·53–1·02; p_{trend}=0·0568), non-cardiovascular mortality (0·84, 0·68–1·04; p_{trend} =0·0038), and total mortality (0·81, 0·68–0·96; p_{trend}<0·0001). The HR for total mortality was lowest for three to four servings per day (0·78, 95% CI 0·69–0·88) compared with the reference group, with no further apparent decrease in HR with higher consumption. When examined separately, fruit intake was associated with lower risk of cardiovascular, non-cardiovascular, and total mortality, while legume intake was inversely associated with non-cardiovascular death and total mortality (in fully adjusted models). For vegetables, raw vegetable intake was strongly associated with a lower risk of total mortality, whereas cooked vegetable intake showed a modest benefit against mortality.

Interpretation Higher fruit, vegetable, and legume consumption was associated with a lower risk of non-cardiovascular, and total mortality. Benefits appear to be maximum for both non-cardiovascular mortality and total mortality at three to four servings per day (equivalent to 375–500 g/day).

Funding Full funding sources listed at the end of the paper (see Acknowledgments).

Introduction

Several guidelines recommend the consumption of five or more servings per day of fruits, vegetables, and legumes.[1,2] This recommendation is largely based on observational data from Europe and the USA and a few studies from Japan and China. Consumption of these foods is higher in

Published Online August 29, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32253-5

See Online/Comment http://dx.doi.org/10.1016/S0140-6736(17)32251-1

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Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 1960, and May 1, 2017, using the terms "fruit" OR "vegetable" OR "legume" OR "dietary pulse" OR "produce" OR "food" OR "diet" AND "cardiovascular" OR "coronary heart disease" OR "ischemic" OR "myocardial" OR "stroke" OR "death" OR "mortality" OR "sudden cardiac death". We used search terms in English but did not apply any language restrictions. We screened papers by title and abstract to identify full-text reports that were relevant to the study aims. We also screened citation lists for these full-text reports to identify other relevant articles. Articles were considered relevant if they reported the relation between fruit, vegetable, or legume intake and cardiovascular events or total mortality. Numerous prospective cohort studies have reported inverse associations between fruit, vegetable and legume intake and cardiovascular events and total mortality, but existing evidence was limited to studies predominantly from European countries, the USA, Japan, and China, with little data available from other regions of the world. Additionally, previous studies have shown that the consumption of fruits, vegetables, and legumes is low among many populations, predominantly those in countries outside Europe or the USA. It is unclear whether these food items are beneficially associated with cardiovascular risk in non-Western countries.

Added value of this study

In our analysis of 135 335 participants from 18 countries, we assessed relationships across a broad range of intakes including very low consumption of fruits and vegetables, and high consumption of legumes. To our knowledge, this is the only global study relating fruit, vegetable, and legume intake to cardiovascular disease events and mortality. The results showed that non-cardiovascular mortality and total mortality are decreased with high intake of fruits, vegetables, and legumes compared with low intake.

Implications of all the available evidence

Many dietary guidelines recommend a minimum of 400 g/day of fruits and vegetables, which might not be achievable globally since fruits and vegetables have previously been shown to be unaffordable in low-income and lower-middle income countries. Our findings that even three servings per day (375 g/day) show similar benefit against the risk of non-cardiovascular and total mortality as higher intakes indicates that optimal health benefits can be achieved with a more modest level of consumption, an approach that is likely to be more affordable in poor countries.

Europe and the USA than other populations[3] and little information is available on any potential associations of lower levels of consumption of fruit and vegetables with cardiovascular disease or deaths outside European or US populations (such as those from the Middle East, South America, Africa, and south Asia). Even in studies from Europe and the USA,[4] the apparent benefits of fruit and vegetable consumption vary substantially (from as large as a 40% relative risk reduction to no benefit) depending on the outcome (myocardial infarction, stroke, or death), exposures reported (fruits, vegetables, or both), or the extent of statistical adjustment for other variables that might relate to cardiovascular disease or death (eg, other dietary variables or socioeconomic status). Moreover, mean consumption of fruit and vegetables in most countries is lower than current recommendations,[3,5] and partly because of the relative unaffordability of fruits and vegetables in poorer countries.[5] Although fruits are mainly consumed fresh in most parts of the world, vegetables are eaten raw or cooked in Europe and the USA, and mostly cooked in Asia and in other parts of the world.

Currently, most dietary guidelines do not differentiate between raw and cooked vegetable intake, despite potential differences in nutritional composition and digestibility.[6,7] Therefore, guidelines that are largely based on European and US data might not necessarily apply to other regions of the world. In this study, we investigated the association of fruit, vegetable, and legume consumption with cardiovascular outcomes and total mortality in a prospective cohort study from 18 countries from seven geographical regions: North America and Europe, South America, the Middle East, south Asia, China, southeast Asia, and Africa. This allowed us to investigate relationships across a broad range of intakes including very low consumption of fruits and vegetables, and high consumption of legumes. Additionally, we examined the associations of raw and cooked vegetable intake independently from each other with cardiovascular disease events and total mortality.

Methods

Study design and sample selection

We did a prospective cohort study (Prospective Urban Rural Epidemiology [PURE]) in individuals aged 35–70 years without cardiovascular disease from 613 communities in 18 low-income, middle-income, and high-income countries (HIC) in seven geographical regions: North America and Europe, South America, the Middle East, south Asia, China, southeast Asia, and Africa. A detailed description of participant, community, and country selection has been published previously[8–11] and is summarised in the appendix (p 3). We considered the heterogeneity of socioeconomic factors and the feasibility of carrying out long-term follow-up when selecting the participating countries. We included three HICs (Canada, Sweden, and United Arab Emirates), seven upper-middle income (UMICs; Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey), four lower-middle income (LMICs; China, Colombia, Iran, and the occupied Palestinian territory) and four low-income countries (LICs; Bangladesh, India, Pakistan, and Zimbabwe), based on gross national income per capita from the World Bank classification for 2006 when the study was initiated. The study was approved by relevant institutional research ethics boards at all sites.

Procedures

At baseline, participants completed dietary assessments using country-specific (region-specific in India), validated food frequency questionnaires (FFQs).[12–22] For countries that had a previously validated FFQ (Canada, China, India, Malaysia, South Africa, Sweden, and Turkey) we used the nutrient databases that were used for the FFQ validation. For countries where a validated FFQ was not available, we developed and validated FFQs using a standard method (appendix p 9). To develop and validate the FFQs, a subgroup of participants from each country completed 24-h dietary recalls for each season (to account for seasonal changes in diet) and a food list was compiled based on the most frequently reported food items. To convert food into nutrients, we constructed country-specific nutrient databases with information about 43 macronutrients and micronutrients that were mainly based on the US Department of Agriculture (USDA) food-composition database (release 18 and 21), modified appropriately with reference to local food composition tables, and supplemented with recipes of locally eaten mixed dishes. The FFQ was administered to the same subgroup of participants in each country and we used Pearson correlation coefficients, using energy adjusted and deattenuated correlations, and weighted κ to validate the FFQs measured against 24-h dietary recalls. Our validation studies showed reasonable agreement between the FFQs and 24-h recalls for fruits (r_s=0·23–0·66) and vegetables (r_s=0·30–0·81) and the concordance rates of classification into the same quartiles ranged from 70% to 74% for fruit and 62% to 79% for vegetables.

See Online for appendix

Potatoes, other tubers, and legumes were not included as vegetables. Fruit and vegetable juices were excluded.

	<1 per day (n=9082)	≥1 to <2 per day (n=19 036)	≥2 to <3 per day (n=35 128)	≥3 to <4 per day (n=24 485)	≥4 to <5 per day (n=14 849)	≥5 to <6 per day (n=9790)	≥6 to <7 per day (n=6945)	≥7 to <8 per day (n=4857)	≥8 per day (n=11 163)
Age (year)	49·0 (41·0–58·0)	49·0 (40·0–58·0)	50·0 (42·0–58·0)	50·0 (42·0–57·0)	50·0 (42·0–58·0)	50·0 (42·0–58·0)	50·0 (43·0–58·0)	50·0 (43·0–58·0)	51·0 (44·0–59·0)
Female sex	5303 (58%)	11 218 (59%)	20 260 (58%)	14 156 (58%)	8592 (58%)	5618 (57%)	4048 (58%)	2862 (59%)	6856 (61%)
Urban location	2901 (32%)	7771 (41%)	16 447 (47%)	13 988 (57%)	9313 (63%)	5976 (61%)	4260 (61%)	3227 (66%)	7417 (66%)
Education level									
Less than graduation from high-school	6027/9031 (66%)	10 514/18 953 (55%)	14 625/35 033 (42%)	8838/24 436 (36%)	5393/14 825 (36%)	3809/9769 (39%)	2693/6933 (39%)	1769/4852 (36%)	3770/11 149 (34%)
High-school graduate	2502/9031 (28%)	6476/18 953 (34%)	15 737/35 033 (45%)	10 791/24 436 (44%)	5795/14 825 (39%)	3315/9769 (34%)	2206/6933 (32%)	1513/4852 (31%)	3395/11 149 (30%)
Some college or more	502/9031 (6%)	1963/18 953 (10%)	4671/35 033 (13%)	4807/24 436 (20%)	3637/14 825 (24%)	2645/9769 (27%)	2034/6933 (29%)	1570/4852 (32%)	3984/11 149 (36%)
Currently a smoker	2676/9031 (29%)	4480/18 953 (24%)	7836/35 033 (22%)	4982/24 436 (20%)	2883/14 825 (19%)	1761/9769 (18%)	1280/6933 (18%)	814/4852 (17%)	1698/11 149 (15%)
High physical activity level*	3253/7388 (36%)	7947/16 738 (42%)	13 817/33 335 (39%)	10 115/23 398 (41%)	5954/14 162 (40%)	4200/9272 (43%)	3168/6560 (46%)	2274/4606 (47%)	5346/10 486 (48%)
Waist-to-hip ratio	0·859 (0·086)	0·865 (0·090)	0·868 (0·081)	0·871 (0·082)	0·877 (0·086)	0·882 (0·086)	0·882 (0·088)	0·881 (0·088)	0·878 (0·088)
Energy intake (kcal/day)†	1442 (1077–1906)	1698 (1322–2205)	1847 (1461–2338)	2017 (1618–2517)	2160 (1726–2698)	2254 (1817–2767)	2363 (1923–2903)	2498 (2036–3054)	2869 (2305–3559)
Vegetable intake (servings per day)	0·27 (0·23)	0·76 (0·39)	1·60 (0·55)	1·86 (0·54)	2·18 (0·75)	2·67 (1·01)	3·13 (1·27)	3·63 (1·49)	4·91 (2·67)
Fruit intake (servings per day)	0·19 (0·22)	0·43 (0·35)	0·62 (0·35)	1·23 (0·60)	1·82 (0·83)	2·27 (1·13)	2·76 (1·40)	3·24 (1·58)	5·21 (3·03)
Legume intake (servings per day)	0·14 (0·16)	0·35 (0·33)	0·30 (0·36)	0·37 (0·41)	0·45 (0·49)	0·53 (0·57)	0·57 (0·60)	0·59 (0·60)	0·71 (0·77)
Starch intake (g/day)	604·8 (465·4)	659·6 (478·3)	507·7 (340·8)	491·8 (318·8)	510·8 (325·1)	506·4 (314·2)	505·0 (306·2)	506·9 (301·0)	544·5 (331·8)
Red meat intake (g/day)	32·8 (58·2)	37·7 (62·4)	57·2 (67·8)	71·6 (73·8)	75·3 (73·0)	83·2 (76·5)	88·0 (74·6)	89·7 (72·3)	93·8 (76·9)
White meat intake (g/day)	16·2 (30·0)	21·3 (33·2)	18·5 (30·6)	24·3 (36·4)	36·7 (47·8)	38·5 (44·9)	42·9 (44·8)	47·9 (48·7)	57·1 (62·2)

Total number of participants=135 335. Data are median (IQR), n (%), n/N (%), or mean (SD). *Defined as ≥3000 metabolic equivalent of task-min per week. †Plausible energy intake between ≥500 kcal/day and ≤5000 kcal/day.

Table 1: **Participants' characteristics divided by number of fruit, vegetable, and legume servings per day**

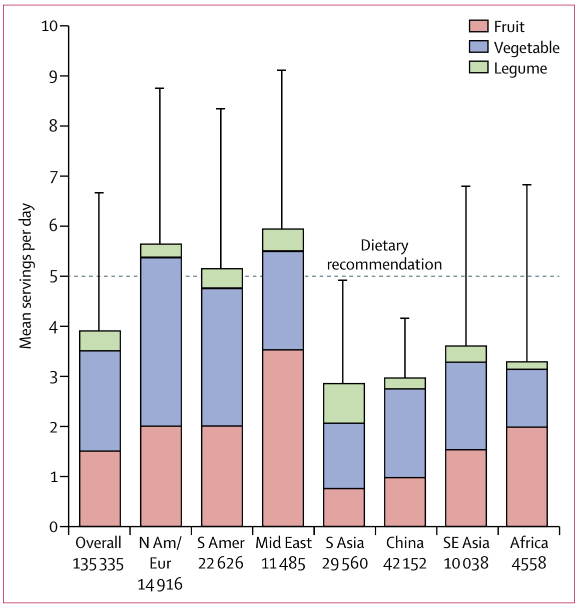


***Figure 1*: Mean fruit, vegetable, and legume intake overall and by geographical region**

Data are from 135 335 individuals. N Am/Eur=North America and Europe: Canada, Poland, and Sweden. S Amer=South America: Argentina, Brazil, Chile, and Colombia. Mid East=Middle East: Iran, occupied Palestinian territory, Turkey, and United Arab Emirates. S Asia=south Asia: Bangladesh, India, and Pakistan. SE Asia=southeast Asia: Malaysia. Africa=South Africa and Zimbabwe.

Legumes included beans, black beans, lentils, peas, chickpeas, and black-eyed peas. Because of inconsistent classification of legumes as a subset of vegetables,[23,24] we grouped total fruit, vegetable, and legume intake into a single food group for our primary analysis (presented in this report) and also present total fruits and vegetables (without legumes) as a separate food group in a secondary analysis (appendix). Although many nutritional qualities of legumes differ from those of vegetables (eg, variable amounts of starch and energy), both legumes and vegetables are good sources of plant protein, fibre, and isoflavones.[23]

We used standardised questionnaires to obtain information about demographic factors, socioeconomic status (education, income, and employment), lifestyle (smoking, physical activity, and alcohol intake), health history and medication use, and family history of cardiovascular disease. Physical assessments included standardised measurements of weight, height, waist and hip circumferences, and blood pressure. Case-report forms, death certificates, medical records and verbal autopsies were used to capture data about major cardiovascular events, and death during follow-up, which were adjudicated centrally in each country by trained physicians using predefined definitions. The follow-up varied based on the date when recruitment began at each site or country. During the follow-up, contact was made with every participant at least every 3 years either by telephone or by a face-to-face visit by the local research team. The median duration of follow-up by country is in the appendix (p 6).

Outcomes

The main clinical outcomes were major cardiovascular disease (defined as death from cardiovascular causes and non-fatal myocardial infarction, stroke, and heart failure), fatal and non-fatal myocardial infarction, fatal and non-fatal strokes, cardiovascular mortality, non-cardiovascular mortality, and total mortality.

Statistical analysis

We computed mean and median estimated fruit, vegetable, and legume intakes in servings overall and by geographical region. One serving was defined as 125 g of fruits or vegetables and 150 g of cooked legumes in accordance with USDA serving sizes. Participants were grouped into categories based on intake values for each dietary exposure (ranging from servings per month to servings per day depending on the dietary exposure). We calculated hazard ratios (HR) using multivariable Cox frailty analysis with random intercepts to account for the correlation of observations within centres (which therefore also accounted for clustering at region and country levels). In a minimally adjusted model, we adjusted for age, sex, and centre as a random effect. The primary model adjusted for age, sex, energy intake, current smoking status, urban or rural location, physical activity, baseline diabetes, education, and other dietary variables (white meat, red meat, bread, and cereal intake), and study centre (as a random effect). For the analyses of fruit intake, we adjusted for vegetable intake, and conversely, analyses of vegetable intake were adjusted for fruit intake. We adjusted for variations in socioeconomic status using education level and household income or wealth index; these produced similar results. The primary analysis did not adjust for obesity, hypertension, or hypercholesterolaemia because these factors might mediate the effects of fruits, vegetables, and legumes on the risk of cardiovascular disease and mortality. We did separate analyses that adjusted for these factors (appendix pp 57–68) and the results were largely similar to the primary model. To test for linear trends, categories of fruit, vegetable, and legume intake were replaced with continuous intake in the Cox frailty regression models. We did interaction tests for fruit, vegetable, and legume intake, and geographical region. Data were analysed with SAS version 9.4.

Role of the funding sources

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (VMi), senior authors (SA and SY), and several co-authors (AM, XZ) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2003, and March 31, 2013, 148 723 participants completed the FFQ, of which 143 934 people had

	<1 per day (n=9082)	≥1 to <2 per day (n=19 036)	≥2 to <3 per day (n=35 128)	≥3 to <4 per day (n=24 485)	≥4 to <5 per day (n=14 849)	≥5 to <6 per day (n=9790)	≥6 to <7 per day (n=6945)	≥7 to <8 per day (n=4857)	≥8 per day (n=11 163)	p_{trend}
Median (IQR) fruit, vegetable, and legume servings per day	0·64 (0·41–0·83)	1·56 (1·30–1·79)	2·52 (2·29–2·75)	3·43 (3·21–3·70)	4·43 (4·19–4·70)	5·46 (5·22–5·72)	6·45 (6·22–6·71)	7·46 (7·22–7·71)	9·99 (8·82–12·15)	NA
Major cardiovascular disease events (n=4784)	373 (4%)	743 (4%)	1391 (4%)	882 (4%)	534 (4%)	267 (3%)	180 (3%)	131 (3%)	283(3%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	1·00 (0·88–1·14)	1·06 (0·94–1·20)	1·00 (0·87–1·14)	1·09 (0·94–1·25)	0·86 (0·73–1·02)	0·84 (0·70–1·02)	0·90 (0·73–1·10)	0·83 (0·70–0·99)	0·0015
Multivariable adjusted	1 (ref)	1·03 (0·89–1·18)	1·09 (0·96–1·25)	1·06 (0·92–1·22)	1·20 (1·02–1·40)	0·95 (0·79–1·14)	0·93 (0·76–1·14)	0·97 (0·77–1·21)	0·90 (0·74–1·10)	0·1301
Myocardial infarction events (n=2143)	164 (2%)	391 (2%)	565 (2%)	375 (2%)	254 (2%)	114 (1%)	77 (1%)	60 (1%)	143 (1%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	1·06 (0·88–1·28)	1·16 (0·97–1·40)	1·14 (0·94–1·38)	1·22 (0·99–1·50)	0·83 (0·65–1·07)	0·80 (0·61–1·07)	0·89 (0·65–1·21)	0·95 (0·65–1·21)	0·0403
Multivariable adjusted	1 (ref)	1·04 (0·85–1·27)	1·15 (0·95–1·40)	1·15 (0·93–1·43)	1·28 (1·02–1·61)	0·87 (0·66–1·14)	0·84 (0·62–1·13)	0·91 (0·65–1·27)	0·99 (0·74–1·31)	0·2033
Stroke events (n=2234)	157 (2%)	283 (1%)	727 (2%)	463 (2%)	233 (2%)	127 (1%)	81 (1%)	59 (1%)	104 (<1%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	1·00 (0·82–1·22)	1·03 (0·85–1·24)	0·99 (0·82–1·21)	1·07 (0·86–1·33)	1·03 (0·80–1·32)	1·00 (0·75–1·33)	1·11 (0·81–1·52)	0·85 (0·65–1·13)	0·5947
Multivariable adjusted	1 (ref)	1·02 (0·82–1·27)	1·05 (0·86–1·29)	1·04 (0·84–1·29)	1·16 (0·92–1·47)	1·12 (0·85–1·47)	1·11 (0·82–1·50)	1·19 (0·84–1·67)	0·92 (0·67–1·25)	0·7092
Cardiovascular death events (n=1649)	215 (2%)	361 (2%)	418 (1%)	245 (1%)	161 (1%)	68 (<1%)	57 (<1%)	43 (<1%)	81 (<1%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	0·81 (0·68–0·97)	0·81 (0·68–0·97)	0·73 (0·60–0·89)	0·77 (0·62–0·96)	0·51 (0·38–0·68)	0·65 (0·48–0·88)	0·73 (0·52–1·03)	0·59 (0·45–0·79)	<0·0001
Multivariable adjusted	1 (ref)	0·81 (0·71–1·06)	0·90 (0·73–1·10)	0·81 (0·65–1·02)	0·91 (0·71–1·17)	0·58 (0·42–0·80)	0·80 (0·57–1·10)	0·90 (0·62–1·31)	0·73 (0·53–1·02)	0·0568
Non-cardiovascular death events (n=3809)	486 (5%)	918 (5%)	1023 (3%)	485 (2%)	284 (2%)	199 (2%)	130 (2%)	80 (2%)	204 (2%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	0·95 (0·85–1·06)	0·80 (0·71–0·89)	0·61 (0·53–0·69)	0·60 (0·52–0·70)	0·65 (0·55–0·78)	0·62 (0·51–0·77)	0·55 (0·43–0·71)	0·56 (0·47–0·67)	<0·0001
Multivariable adjusted	1 (ref)	1·05 (0·93–1·19)	0·91 (0·80–1·03)	0·77 (0·66–0·89)	0·80 (0·68–0·95)	0·87 (0·71–1·05)	0·87 (0·70–1·09)	0·80 (0·62–1·05)	0·84 (0·68–1·04)	0·0038
Mortality events (n=5796)	736 (8%)	1371 (7%)	1529 (4%)	772 (3%)	468 (3%)	286 (3%)	198 (3%)	131 (3%)	305 (3%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	0·92 (0·84–1·01)	0·81 (0·74–0·89)	0·65 (0·58–0·74)	0·65 (0·58–0·74)	0·62 (0·53–0·71)	0·63 (0·54–0·75)	0·61 (0·50–0·74)	0·58 (0·50–0·74)	<0·0001
Multivariable adjusted	1 (ref)	1·01 (0·91–1·12)	0·91 (0·82–1·01)	0·78 (0·69–0·88)	0·83 (0·72–0·95)	0·78 (0·66–0·91)	0·84 (0·70–1·00)	0·83 (0·67–1·02)	0·81 (0·68–0·96)	0·0001

Total number of participants is 135 335. Data are n (%) or hazard ratio (95% CI) except where otherwise stated. Crude event rates are shown. For this analysis, the group with intake <1 serving per day was used as the reference (ref) group that all other groups were compared with. Additional sensitivity analyses with waist-to-hip ratio, hypertension status, and statin medication used in the model did not substantially change estimates of association (appendix). NA=not applicable. Major cardiovascular disease events=death from cardiovascular causes and non-fatal myocardial infarction, stroke, and heart failure. Multivariable adjusted=adjusted for age, sex, centre (random effect), energy intake, current smoker, diabetes, urban or rural location, physical activity, education level, and tertiles of white meat, red meat, breads, and cereals intake.

***Table 2*: Association of number of fruit, vegetable, and legume servings per day with cardiovascular outcomes and mortality**

plausible energy intake (500–5000 kcal/day) and were not missing information about their age and sex. We excluded 7369 people with a history of cardiovascular disease at baseline and 1230 people for whom follow-up information was not available. The remaining 135 335 individuals were included in this analysis (appendix p 7). For the current analysis, we included all unrefuted outcome events in the PURE study database through March 31, 2017.

People who consumed more fruits, vegetables, and legumes had higher education, higher levels of physical activity, lower rates of smoking, and higher energy, red meat and white meat intake, and were more likely to live in urban areas (table 1). Overall, mean fruit, vegetable, and legume intakes were 1·51 (SD 1·77), 2·01 (1·55), and 0·40 (0·48) servings per day, respectively. Combined mean fruit, vegetable, and legume intake was 3·91 (2·77) servings per day (figure 1).

During a median follow-up of 7·4 years (IQR 5·5–9·3), there were 4784 major cardiovascular disease events recorded (table 2). Higher total fruit, vegetable, and legume intake was inversely associated with major cardiovascular disease, myocardial infarction, cardiovascular mortality, non-cardiovascular mortality, and total mortality in the models adjusted for age, sex, and centre (as a random effect; table 2). Following multivariable adjustment, the associations were

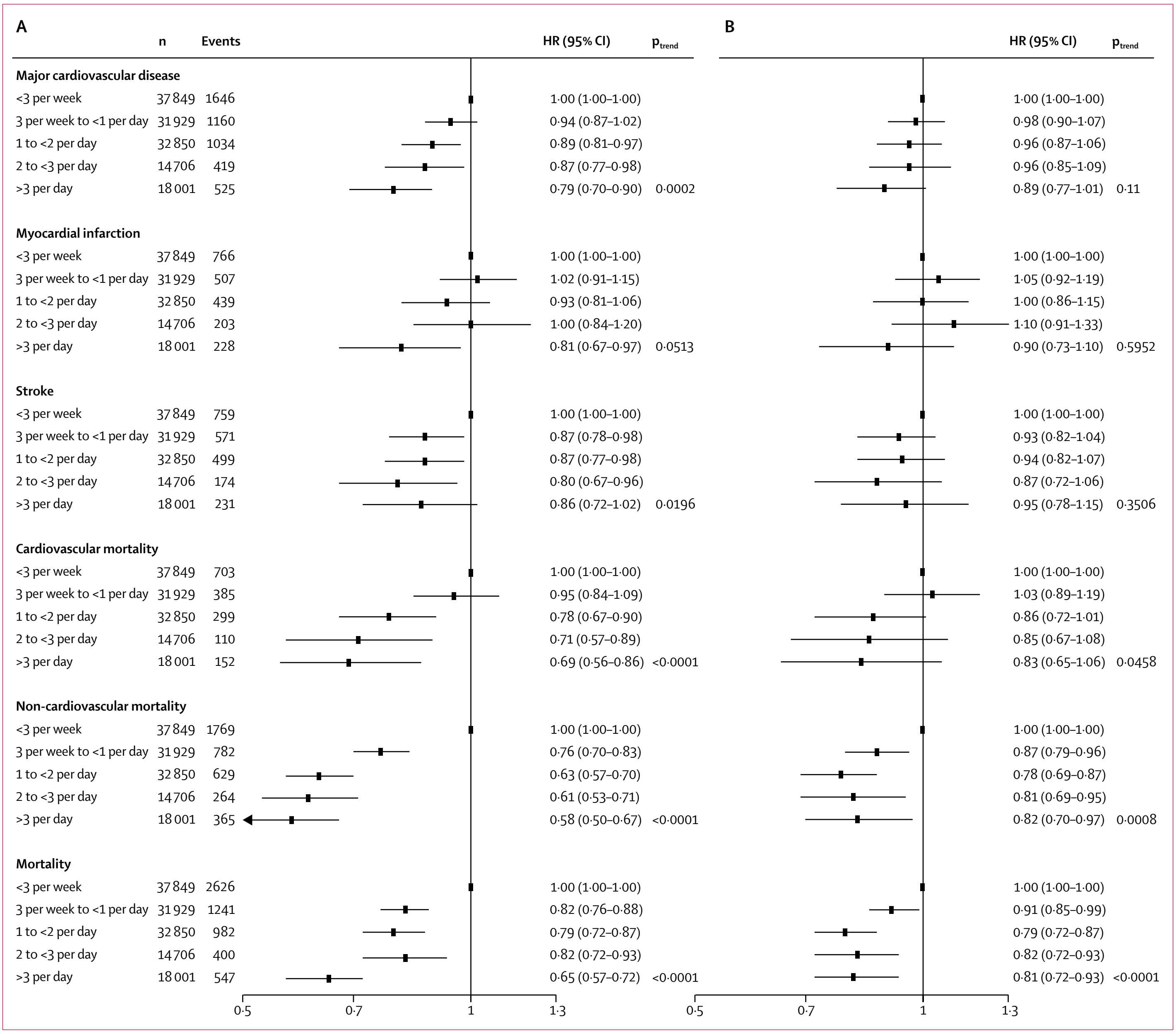
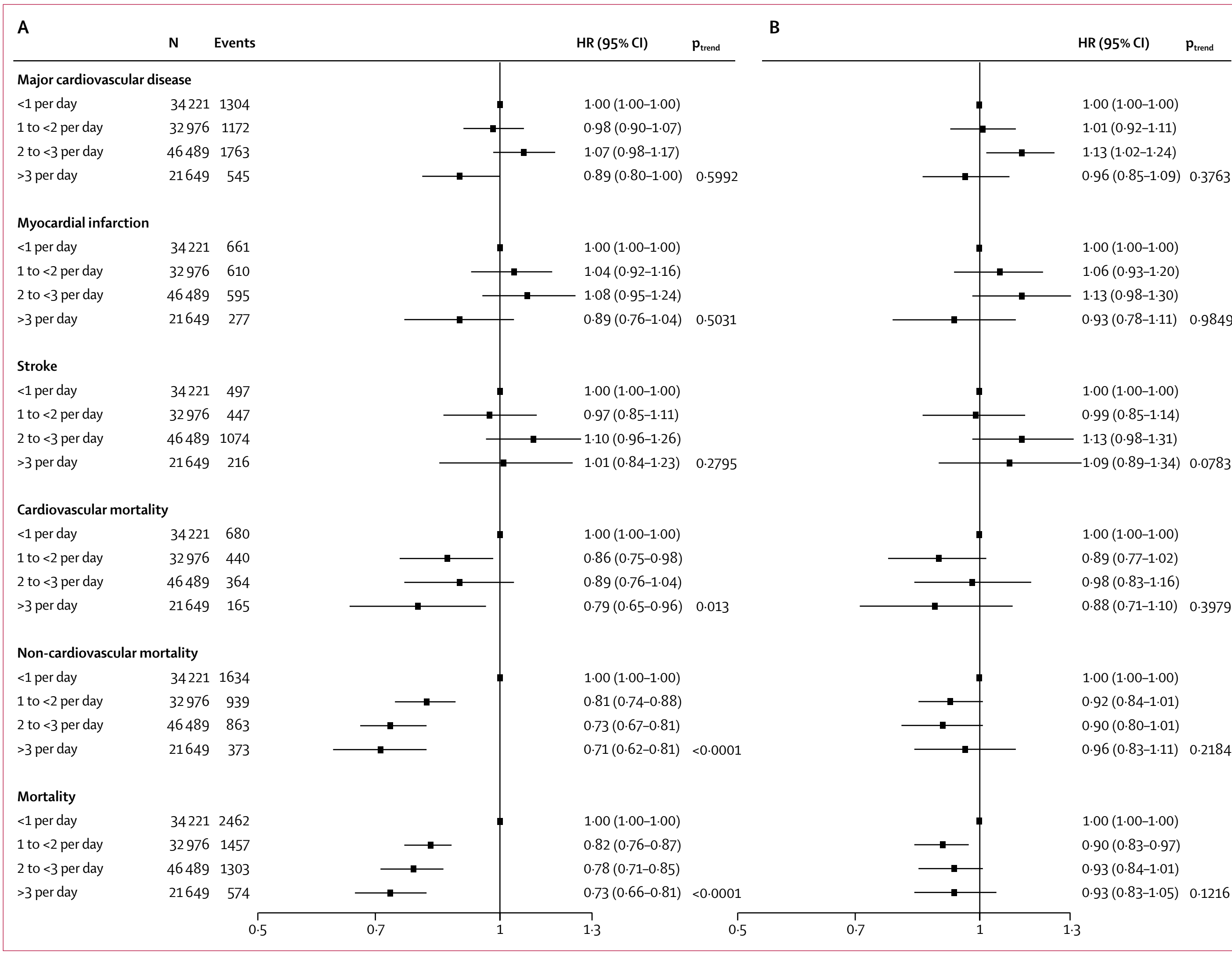


***Figure 2*: Association of fruit intake with cardiovascular outcomes and mortality**

(A) Adjusted for age, sex, and centre (random effect). (B) Adjusted for age, sex, centre (random effect), energy intake, current smoker, diabetes, urban or rural location, physical activity, education level, and tertiles of white meat, red meat, and intake of breads, cereals, and vegetables. Crude event rates are shown. Additional sensitivity analyses with waist-to-hip ratio, hypertension status, and statin medication used in the model did not substantially change estimates of association (appendix). HR=hazard ratio. Major cardiovascular disease events=death from cardiovascular causes and non-fatal myocardial infarction, stroke, and heart failure.

markedly attenuated and only non-cardiovascular mortality and total mortality remained significant, with a non-significant trend for cardiovascular mortality (table 2). The HR for total mortality was lowest for three to four servings per day (0·78, 95% CI 0·69–0·88) compared with the reference group, with no further apparent decrease in HR with higher consumption. Total fruit, vegetable, and legume intake was inversely associated with total mortality in most geographical regions (south Asia, China, North America and Europe, the Middle East, and South America; appendix pp 35–36). Similarly, total fruit and vegetable intake was associated with major cardiovascular disease, myocardial infarction, cardiovascular mortality, non-cardiovascular mortality and total mortality in the age-adjusted and sex-adjusted models, and with lower non-cardiovascular mortality and total mortality in the fully adjusted models.

 www.thelancet.com **Published online August 29, 2017 http://dx.doi.org/10.1016/S0140-6736(17)32253-5**



	N	Events	A: HR (95% CI)	A: p_{trend}	B: HR (95% CI)	B: p_{trend}
Major cardiovascular disease						
<1 per day	34 221	1304	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 to <2 per day	32 976	1172	0·98 (0·90–1·07)		1·01 (0·92–1·11)	
2 to <3 per day	46 489	1763	1·07 (0·98–1·17)		1·13 (1·02–1·24)	
>3 per day	21 649	545	0·89 (0·80–1·00)	0·5992	0·96 (0·85–1·09)	0·3763
Myocardial infarction						
<1 per day	34 221	661	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 to <2 per day	32 976	610	1·04 (0·92–1·16)		1·06 (0·93–1·20)	
2 to <3 per day	46 489	595	1·08 (0·95–1·24)		1·13 (0·98–1·30)	
>3 per day	21 649	277	0·89 (0·76–1·04)	0·5031	0·93 (0·78–1·11)	0·9849
Stroke						
<1 per day	34 221	497	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 to <2 per day	32 976	447	0·97 (0·85–1·11)		0·99 (0·85–1·14)	
2 to <3 per day	46 489	1074	1·10 (0·96–1·26)		1·13 (0·98–1·31)	
>3 per day	21 649	216	1·01 (0·84–1·23)	0·2795	1·09 (0·89–1·34)	0·0783
Cardiovascular mortality						
<1 per day	34 221	680	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 to <2 per day	32 976	440	0·86 (0·75–0·98)		0·89 (0·77–1·02)	
2 to <3 per day	46 489	364	0·89 (0·76–1·04)		0·98 (0·83–1·16)	
>3 per day	21 649	165	0·79 (0·65–0·96)	0·013	0·88 (0·71–1·10)	0·3979
Non-cardiovascular mortality						
<1 per day	34 221	1634	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 to <2 per day	32 976	939	0·81 (0·74–0·88)		0·92 (0·84–1·01)	
2 to <3 per day	46 489	863	0·73 (0·67–0·81)		0·90 (0·80–1·01)	
>3 per day	21 649	373	0·71 (0·62–0·81)	<0·0001	0·96 (0·83–1·11)	0·2184
Mortality						
<1 per day	34 221	2462	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 to <2 per day	32 976	1457	0·82 (0·76–0·87)		0·90 (0·83–0·97)	
2 to <3 per day	46 489	1303	0·78 (0·71–0·85)		0·93 (0·84–1·01)	
>3 per day	21 649	574	0·73 (0·66–0·81)	<0·0001	0·93 (0·83–1·05)	0·1216

***Figure 3*: Association of vegetable intake with cardiovascular outcomes and mortality**

(A) Adjusted for age, sex, and centre (random effect). (B) Adjusted for age, sex, centre (random effect), energy intake, current smoker, diabetes, urban/rural location, physical activity, education level, and tertiles of white meat, red meat, and intake of breads, cereals, and fruit. Crude event rates are shown. Additional sensitivity analyses with waist-to-hip ratio, hypertension status, and statin medication used in the model did not substantially change estimates of association (appendix). HR=hazard ratio. Major cardiovascular disease events=death from cardiovascular causes and nonfatal myocardial infarction, stroke, and heart failure.

After adjusting for age and sex, fruit consumption was inversely associated with the risk of major cardiovascular disease, stroke, cardiovascular mortality, non-cardiovascular mortality, and total mortality (figure 2). The associations were markedly attenuated after adjusting for additional lifestyle and dietary factors and only cardiovascular mortality, non-cardiovascular mortality, and total mortality remained significant (figure 2). An inverse association between higher fruit intake and the risk of total mortality was observed in south Asia, China, the Middle East, and South America (appendix pp 37–38).

In the age-adjusted and sex-adjusted models, vegetable intake was inversely associated with cardiovascular mortality, non-cardiovascular mortality, and total mortality (figure 3). After adjustment for additional covariates, vegetable intake was not significantly associated with these outcomes (figure 3). Similarly, no significant association was observed between vegetable intake and total mortality in most geographical regions (China, southeast Asia, Africa, the Middle East, and South America), but a beneficial association was shown in south Asia, and North America and Europe (appendix pp 39–40).

Legume consumption was inversely associated with cardiovascular mortality, non-cardiovascular mortality, and total mortality in the minimally adjusted models and with non-cardiovascular mortality and total mortality in the fully adjusted models (figure 4).

The percentage of total vegetable intake consumed as raw vegetables was low in south Asia, Africa, and southeast

	<1 serving per month (n=24 054)	1 serving per month to <1 per week (n=9086)	1 to <3 servings per week (n=15 410)	3 servings per week to <1 per day (n=16 263)	1 to 2 servings per day (n=15 818)	>2 servings per day (n=12 552)	p_{trend}
Median (IQR) raw vegetable servings per day	0·00 (0·00–0·00)	0·08 (0·05–0·11)	0·25 (0·20–0·33)	0·67 (0·52–0·82)	1·42 (1·19–1·66)	2·82 (2·35–3·61)	NA
Major cardiovascular disease events (n=3085)	1147 (5%)	313 (3%)	459 (3%)	477 (3%)	422 (3%)	267 (2%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	0·97 (0·84–1·12)	0·89 (0·77–1·03)	0·93 (0·79–1·09)	0·88 (0·74–1·05)	0·71 (0·58–0·87)	0·0056
Multivariable adjusted	1 (ref)	0·96 (0·82–1·13)	0·86 (0·73–1·01)	0·92 (0·77–1·11)	0·92 (0·76–1·12)	0·79 (0·63–1·00)	0·1303
Mortality events (n=4640)	2329 (10%)	480 (5%)	670 (4%)	536 (3%)	396 (3%)	229 (2%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	0·75 (0·68–0·84)	0·66 (0·59–0·74)	0·63 (0·55–0·72)	0·59 (0·50–0·70)	0·46 (0·38–0·56)	<0·0001
Multivariable adjusted	1 (ref)	0·86 (0·75–0·97)	0·77 (0·68–0·89)	0·76 (0·65–0·89)	0·81 (0·68–0·97)	0·69 (0·55–0·85)	0·0009

Total number of participants is 93 183. Data are n (%) or hazard ratio (95% CI) unless otherwise stated. Crude event rates are shown. For this analysis, the group with intake <1 serving per day was used as the reference (ref) group that all other groups were compared with. Sensitivity analyses adjusting for waist-to-hip ratio, hypertension status, and statin medication, and including the participants from China (by assuming that total vegetable intake was consumed as cooked vegetables) did not substantially change estimates of association (appendix). NA=not applicable. Major cardiovascular disease events=death from cardiovascular causes and non-fatal myocardial infarction, stroke, and heart failure. Multivariable adjusted=adjusted for age, sex, centre (random effect), energy intake, current smoker, diabetes, urban or rural location, physical activity, education level, and tertiles of white meat, red meat, breads, cereals, and fruit intake. Does not include data from China (n=42 152) because the food frequency questionnaires used in this country did not differentiate between raw and cooked vegetables.

***Table 3*: Association of raw vegetable intake with cardiovascular disease and mortality**

	<3 servings per week (n=20 890)	3 servings per week to <1 per day (n=33 395)	1 to 2 servings per day (n=25 813)	>2 servings per day (n=13 085)	p_{trend}
Median (IQR) cooked vegetable servings per day	0·26 (0·16–0·34)	0·68 (0·55–0·83)	1·34 (1·15–1·61)	2·66 (2·27–3·33)	NA
Major cardiovascular disease events (n=3085)	685 (3%)	1083 (3%)	811 (3%)	506 (4%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	1·02 (0·92–1·13)	0·98 (0·88–1·10)	1·06 (0·93–1·21)	0·6180
Multivariable adjusted	1 (ref)	1·10 (0·98–1·22)	1·07 (0·94–1·21)	1·17 (1·01–1·36)	0·0853
Mortality events (n=4640)	661 (2%)	610 (2%)	595 (1%)	277 (1%)	NA
Adjusted for age, sex, and centre (random effect)	1 (ref)	0·88 (0·82–0·95)	0·74 (0·67–0·80)	0·72 (0·65–0·80)	<0·0001
Multivariable adjusted	1 (ref)	0·99 (0·91–1·08)	0·86 (0·77–0·95)	0·91 (0·80–1·03)	0·0110

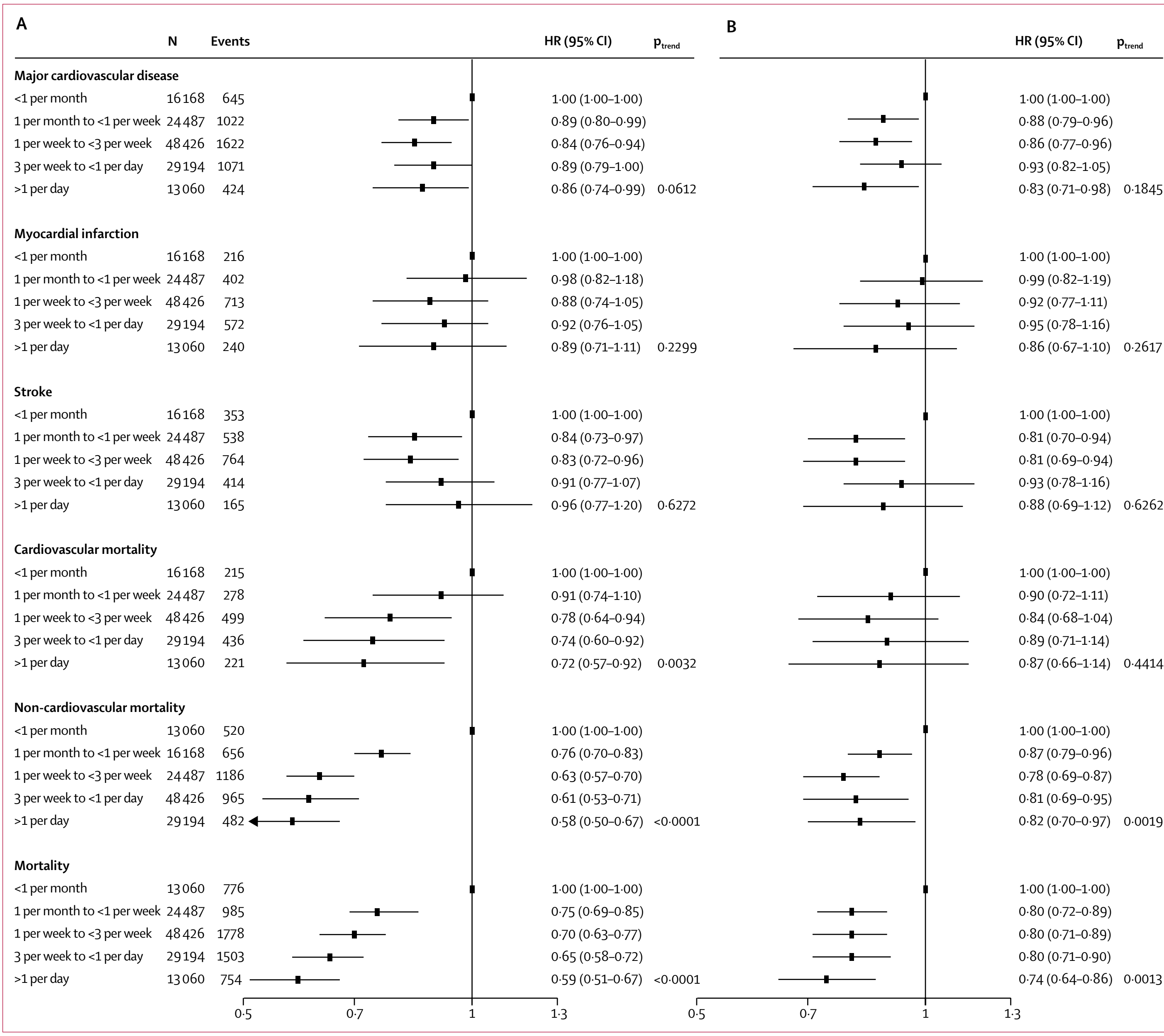
Total number of participants is 93 183. Data are n (%) or hazard ratio (95% CI) unless otherwise stated. Crude event rates are shown. For this analysis, the group with intake <1 serving per day was used as the reference (ref) group that all other groups were compared with. Sensitivity analyses adjusting for waist-to-hip ratio, hypertension status, and statin medication, and including the participants from China (by assuming that total vegetable intake was consumed as cooked vegetables) did not substantially change estimates of association (appendix). NA=not applicable. Major cardiovascular disease events=death from cardiovascular causes and non-fatal myocardial infarction, stroke, and heart failure. Multivariable adjusted=adjusted for age, sex, centre (random effect), energy intake, current smoker, diabetes, urban or rural location, physical activity, education level, and tertiles of white meat, red meat, breads, cereals, and fruit intake. Does not include data from China (n=42 152) because the food frequency questionnaires used in this country did not differentiate between raw and cooked vegetables.

***Table 4*: Association of cooked vegetable intake with cardiovascular disease and mortality**

Asia (figure 5). In the fully adjusted models, both raw and cooked vegetable intakes were inversely associated with total mortality (tables 3, 4). The risk of major cardiovascular disease was inversely associated with the level of raw vegetable intake, but not cooked vegetable intake (tables 3, 4). A non-significant inverse trend for the level of raw vegetable intake and risk of major cardiovascular disease was observed, but no association was shown for cooked vegetable intake.

Discussion

In this large, international prospective cohort study, we showed that greater fruit, vegetable, and legume intake was associated with a lower risk of major cardiovascular disease, myocardial infarction, cardiovascular mortality, non-cardiovascular mortality, and total mortality in the analyses adjusted for age and sex. With multivariable adjustment (demographic characteristics, lifestyle, health history, and dietary factors), the associations remained significant for non-cardiovascular mortality and total mortality, with a non-significant trend for lower cardiovascular mortality. Furthermore, an intake of three to four servings per day (equivalent to 375–500 g/day) was as beneficial as higher amounts of intake in reducing total mortality. Our findings indicate that even relatively moderate intakes of fruits, vegetables and legumes might lower the risk of death. A meta-analysis[4] reported the steepest reduction in risk of total mortality with up to 400 g



Outcome / legume intake	N	Events	A: HR (95% CI)	A: p_{trend}	B: HR (95% CI)	B: p_{trend}
Major cardiovascular disease						
<1 per month	16 168	645	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 per month to <1 per week	24 487	1022	0·89 (0·80–0·99)		0·88 (0·79–0·96)	
1 per week to <3 per week	48 426	1622	0·84 (0·76–0·94)		0·86 (0·77–0·96)	
3 per week to <1 per day	29 194	1071	0·89 (0·79–1·00)		0·93 (0·82–1·05)	
>1 per day	13 060	424	0·86 (0·74–0·99)	0·0612	0·83 (0·71–0·98)	0·1845
Myocardial infarction						
<1 per month	16 168	216	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 per month to <1 per week	24 487	402	0·98 (0·82–1·18)		0·99 (0·82–1·19)	
1 per week to <3 per week	48 426	713	0·88 (0·74–1·05)		0·92 (0·77–1·11)	
3 per week to <1 per day	29 194	572	0·92 (0·76–1·05)		0·95 (0·78–1·16)	
>1 per day	13 060	240	0·89 (0·71–1·11)	0·2299	0·86 (0·67–1·10)	0·2617
Stroke						
<1 per month	16 168	353	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 per month to <1 per week	24 487	538	0·84 (0·73–0·97)		0·81 (0·70–0·94)	
1 per week to <3 per week	48 426	764	0·83 (0·72–0·96)		0·81 (0·69–0·94)	
3 per week to <1 per day	29 194	414	0·91 (0·77–1·07)		0·93 (0·78–1·16)	
>1 per day	13 060	165	0·96 (0·77–1·20)	0·6272	0·88 (0·69–1·12)	0·6262
Cardiovascular mortality						
<1 per month	16 168	215	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 per month to <1 per week	24 487	278	0·91 (0·74–1·10)		0·90 (0·72–1·11)	
1 per week to <3 per week	48 426	499	0·78 (0·64–0·94)		0·84 (0·68–1·04)	
3 per week to <1 per day	29 194	436	0·74 (0·60–0·92)		0·89 (0·71–1·14)	
>1 per day	13 060	221	0·72 (0·57–0·92)	0·0032	0·87 (0·66–1·14)	0·4414
Non-cardiovascular mortality						
<1 per month	13 060	520	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 per month to <1 per week	16 168	656	0·76 (0·70–0·83)		0·87 (0·79–0·96)	
1 per week to <3 per week	24 487	1186	0·63 (0·57–0·70)		0·78 (0·69–0·87)	
3 per week to <1 per day	48 426	965	0·61 (0·53–0·71)		0·81 (0·69–0·95)	
>1 per day	29 194	482	0·58 (0·50–0·67)	<0·0001	0·82 (0·70–0·97)	0·0019
Mortality						
<1 per month	13 060	776	1·00 (1·00–1·00)		1·00 (1·00–1·00)	
1 per month to <1 per week	24 487	985	0·75 (0·69–0·85)		0·80 (0·72–0·89)	
1 per week to <3 per week	48 426	1778	0·70 (0·63–0·77)		0·80 (0·71–0·89)	
3 per week to <1 per day	29 194	1503	0·65 (0·58–0·72)		0·80 (0·71–0·90)	
>1 per day	13 060	754	0·59 (0·51–0·67)	<0·0001	0·74 (0·64–0·86)	0·0013

Figure 4: **Association of legume intake with cardiovascular outcomes and mortality**
(A) Adjusted for age, sex, and centre (random effect). (B) Adjusted for age, sex, centre (random effect), energy intake, current smoker, diabetes, urban/rural location, physical activity, education level, and tertiles of white meat, red meat, and intake of breads and cereals. Crude event rates are shown. Additional sensitivity analyses with waist-to-hip ratio, hypertension status, and statin medication used in the model did not substantially change estimates of association (appendix). HR=hazard ratio. Major cardiovascular disease events=death from cardiovascular causes and nonfatal myocardial infarction, stroke, and heart failure.

of fruits and vegetables per day (equivalent to 3·2 servings in our study), with modest additional benefit for intake above this level (relative risk [RR] 0·76, 95% CI 0·73–0·79 for 400 g/day and RR 0·69, 0·66–0·73 for 800 g/day), which is consistent with our findings.

We showed an 11% lower risk of major cardiovascular disease for the highest fruit intake category compared with the lowest intake category. Our findings are consistent with those from a meta-analysis[4] which showed a beneficial effect (RR 0·87, 95% CI 0·82–0·92) for the prevention of cardiovascular disease. Our results suggest a more modest effect on stroke than some, but not all, previous studies.[4,25] Fewer studies have investigated the association between fruit intake and stroke compared with cardiovascular disease or coronary heart disease. Not all studies of cardiovascular disease reported on both stroke and myocardial infarction, and some reported on only one outcome. This might be partly due to the varying

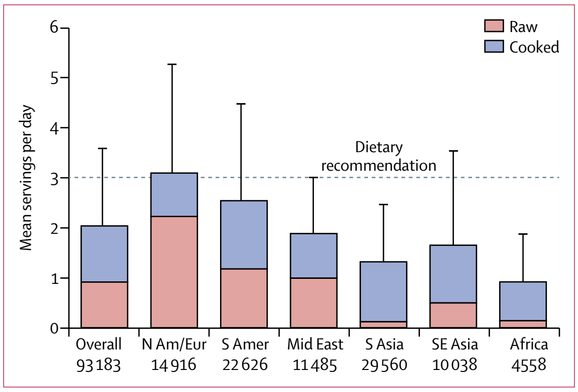


***Figure 5*: Mean raw and cooked vegetable intake overall and by geographical region**

Data are from 93 183 participants, not including those from China (n=42 152) because the food frequency questionnaires used in this country did not differentiate between raw and cooked vegetables. N Am/Eur=North America and Europe: Canada, Poland, and Sweden. S Amer=South America: Argentina, Brazil, Chile, and Colombia. Mid East=Middle East: Iran, occupied Palestinian territory, Turkey, and United Arab Emirates. S Asia=south Asia: Bangladesh, India, and Pakistan. SE Asia=southeast Asia: Malaysia. Africa=South Africa and Zimbabwe.

goals of different studies, but could also be due to a data-derived emphasis about which outcome to report (with the potential that the outcome and exposure with the greater effect size might have been selectively reported or emphasised). Among studies with a similar range of fruit intake as our PURE study, most reported a nominal reduction in the risk of stroke including the Health Professionals Follow-up study,[26] the Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands study,[7] and the Multiethnic Cohort study.[27] Our findings for fruit and cardiovascular mortality and total mortality are in keeping with results from most previous prospective studies.[4,25] We showed a 14% and 21% lower risk of these outcomes when one to two daily servings (equivalent to 125–250 g/day) of fruit were consumed, and intake above this level had little added benefit on risk lowering.

Our finding of a minimal decrease in the risk of major cardiovascular disease and total mortality with higher vegetable intake is consistent with many earlier studies, although substantial heterogeneity in the results of different studies has been reported in a meta-analysis;[4] and, only three of the 18 cohorts included in the meta-analysis reported a robust, inverse association between vegetable intake and cardiovascular disease.[28–30] Among studies with similar daily vegetable intake to the PURE study, the effect estimates for cardiovascular disease, stroke, and total mortality were similar to those in our study.[26–32] Collectively, these data indicate that the association of total vegetable intake and these outcomes is much more modest than generally assumed.

Vegetables might be consumed raw or cooked and the cooking process might alter the bioavailability of nutrients (such as phytochemicals, vitamins, minerals, and fibre), and digestibility. Some evidence suggests that cooking vegetables can degrade nutrient and enzyme content and possibly create harmful byproducts.[33] However, for some nutrients such as lycopene and β carotene, their bioavailability might be enhanced by cooking.[34,35] Little information is available on the effect of raw vegetable intake on cardiovascular disease and total mortality in low-income and middle-income countries. In a cohort of 451 151 participants from ten European countries,[31] both raw and cooked vegetable intakes were inversely associated with risk of mortality, but a stronger beneficial effect was noted for raw vegetable consumption. Additionally, beneficial associations of raw vegetable intake with total mortality, ischaemic heart disease,[36] and ischaemic stroke[7] have been reported. Our findings of a trend towards greater beneficial associations for raw vegetable intake and major cardiovascular disease and total mortality are consistent with some previous reports,[31] but differ from a meta-analysis that showed similar beneficial effects for raw and cooked vegetable intake and the risk of mortality (RR 0·88, 95% CI 0·79–0·98 for raw vegetables and 0·87, 0·80–0·94 for cooked).[4] However, a key limitation of this meta-analysis was that few studies examined raw and cooked vegetable intakes separately within the same study, which can lead to additional confounding (two studies on both raw and cooked vegetables and three on cooked vegetables only).

We found that higher legume consumption was associated with a lower risk of major cardiovascular disease, cardiovascular mortality, non-cardiovascular mortality and total mortality, although only the associations with non-cardiovascular mortality and total mortality were significant after full adjustment. A meta-analysis showed that legume consumption reduced the risk of ischaemic heart disease, but not stroke.[37] However, this meta-analysis included data from only six cohorts, predominantly in North America and Europe, with little data from other regions. Furthermore, the consumption of legumes was low in these studies (eg, <25 g/day) compared with our study (overall mean legume intake of 60 g/day). Legumes contribute a substantial amount of energy and protein for many populations in south Asia, Africa, and Latin America,[38] which are included in PURE. In Costa Rica, higher legume intake (>86 g/day *vs* <86 g/month) was associated with a 38% lower risk of myocardial infarction,[39] which is consistent with our findings. Legumes are frequently consumed as an alternative to meat, and higher glycaemic grains and starches (eg, pasta and white bread), and might be beneficial as a replacement for these foods.[37,40,41] Overall, our findings suggest that higher legume consumption is associated with lower mortality in populations.

Several mechanisms have been proposed to explain the lower risk of cardiovascular disease with higher consumption of fruits, vegetables, and legumes. One explanation is that antioxidants and polyphenols in fruits and vegetables, such as vitamin C, vitamin E, and carotenoids, might prevent lipid oxidation in arterial vessel walls,[42] lower blood pressure,[43,44] and improve endothelial function.[45] Several studies have reported inverse associations between potassium[46] and magnesium[47] with blood pressure. Fruits and vegetables are good sources of dietary fibre, which has been shown to reduce the insulin response to carbohydrates,[48] and decrease total and LDL cholesterol.[49] Similarly, legumes contain fibre and phytochemicals, and legume consumption has been shown to reduce blood pressure, total and LDL cholesterol, and triglycerides.[50]

Our study included data from geographical regions such as the Middle East, South America, Africa, south Asia, and southeast Asia from which little or no data are available on the associations between fruits, vegetables, and legume intake and cardiovascular disease or deaths. Additional strengths of this study included the prospective design, the large sample size, the use of validated, country-specific FFQs to estimate intake, the broad range of intake of fruits, vegetables, and legumes (0 to >1000 g/day), and standardised methods to collect and adjudicate events. Our study also had some limitations. First, fruit, vegetable, and legume consumption was measured using validated country-specific FFQs at baseline and their consumption was assumed to remain unchanged during follow-up. Consequently, measurement errors might have occurred that would probably have resulted in an underestimation of the relationship between dietary intake and cardiovascular disease and mortality. Second, we did not examine the associations of the different types of fruits and vegetables versus cardiovascular disease or mortality; the power to detect these associations was low since such data were not available from China (which removed about 40% of the study population), and the numbers of events per type of fruits and vegetables was relatively low. Furthermore, there were additional confounders as the consumption of different types of vegetables and fruits varied by region, and those consuming low amounts of one vegetable or fruit might have consumed large amounts of another fruit or vegetable. Controlling for such factors requires even more events and therefore the current results are not robust. Third, environmental factors (use of pesticides and herbicides, and water contamination) that might affect the nutritional quality of fruits, vegetables, and legumes were not measured and might have contributed to the differences between our study and previous studies. Fourth, the methods of cultivation, types of fruits and vegetables commonly consumed, and cooking methods (eg, frying *vs* other methods) might have varied across countries. Fifth, in observational studies, the possibility of residual confounding from unmeasured or imprecise measurement of covariates cannot be completely ruled out. This is exemplified by the near halving of apparent associations in the fully adjusted model compared with the minimally adjusted model, and suggests that part of the apparent large benefits in some previous studies might have been due to incomplete adjustment. Sixth, some event misclassification cannot be ruled out. However, the number of misclassified events was probably minimal, as most events were ascertained using supporting documents and adjudicated using standardised definitions. Last, because of the low number of events in some geographical regions, our findings within the geographical regions of the Middle East, Southeast Asia, and North America and Europe are presently not robust. However, we intend to re-examine these relationships in the future when more participants have been enrolled (the study has now nearly enrolled 200 000 people) and longer follow-up will be available. Nevertheless, to our knowledge, this is the first study to report on the associations of fruit, vegetable, and legume intake with cardiovascular risk in countries at varying economic levels and from different regions.

In summary, our results show that higher fruit, vegetable, and legume intake is associated with a lower risk of non-cardiovascular mortality and total mortality, with a non-significant trend for cardiovascular mortality, in a global population. Previous research[4] and many dietary guidelines in North America and Europe[2] recommended intake ranging from 400 to 800 g/day, but these targets are unaffordable for most individuals in LIC and LMIC.[5] Even a small reduction in the recommendation from 400 to 375 g/day may have important implications on household spending and food security in poorer countries. Our findings that even three servings per day (375 g/day) show similar benefit against non-cardiovascular and total mortality as higher intakes and trends towards benefit for cardiovascular mortality, indicate that optimal health benefits can be achieved with a more modest level of consumption, an approach that is likely to be much more affordable.

Contributors

VMi and AM designed the study, were involved in data management and statistical analysis, and wrote the first and subsequent drafts of the report. MD developed and validated the country-specific food frequency questionnaires, supervised the collection of dietary information, and commented on drafts of the report. SR coordinated the worldwide Prospective Urban Rural Epidemiology (PURE) study and reviewed and commented on drafts of the report. XZ and SIB contributed to the statistical analysis and reviewed and commented on drafts of the report. KT was the co-principal investigator of PURE and reviewed and commented on drafts of the report. SY designed the study, conceived and initiated PURE, supervised its conduct and data analysis, and provided comments on all drafts. All other authors coordinated the study, collected data in their respective countries, and provided comments on drafts of the report.

Declaration of interests

We declare no competing interests.

Acknowledgments

SY is supported by the Heart & Stroke Foundation/Marion W. Burke Chair in Cardiovascular Disease. The PURE Study is an investigator-initiated study funded by the Population Health Research Institute, the Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation of Ontario, support from CIHR's Strategy for Patient Oriented Research (SPOR) through the Ontario SPOR Support Unit, as well as the Ontario Ministry of Health and Long-Term Care and through unrestricted grants from several pharmaceutical companies, with major contributions from AstraZeneca (Canada), Sanofi-Aventis

(France and Canada), Boehringer Ingelheim (Germany and Canada), Servier, and GlaxoSmithkline, and additional contributions from Novartis and King Pharma and from various national or local organisations in participating countries; these include: Argentina: Fundacion ECLA; Bangladesh: Independent University, Bangladesh and Mitra and Associates; Brazil: Unilever Health Institute, Brazil; Canada: Public Health Agency of Canada and Champlain Cardiovascular Disease Prevention Network; Chile: Universidad de la Frontera; China: National Center for Cardiovascular Diseases; Colombia: Colciencias, grant number 6566-04-18062; India: Indian Council of Medical Research; Malaysia: Ministry of Science, Technology and Innovation of Malaysia, grant numbers 100 - IRDC/BIOTEK 16/6/21 (13/2007) and 07-05-IFN-BPH 010, Ministry of Higher Education of Malaysia grant number 600 - RMI/LRGS/5/3 (2/2011), Universiti Teknologi MARA, Universiti Kebangsaan Malaysia (UKM-Hejim-Komuniti-15-2010); occupied Palestinian territory: the UN Relief and Works Agency for Palestine Refugees in the Near East, occupied Palestinian territory; International Development Research Centre, Canada; Philippines: Philippine Council for Health Research & Development; Poland: Polish Ministry of Science and Higher Education grant number 290/W-PURE/2008/0, Wroclaw Medical University; Saudi Arabia: the Deanship of Scientific Research at King Saud University, Riyadh, Saudi Arabia (research group number RG -1436-013); South Africa: the North-West University, SANPAD (SA and Netherlands Programme for Alternative Development), National Research Foundation, Medical Research Council of SA, The SA Sugar Association (SASA), Faculty of Community and Health Sciences (UWC); Sweden: grants from the Swedish state under the Agreement concerning research and education of doctors; the Swedish Heart and Lung Foundation; the Swedish Research Council; the Swedish Council for Health, Working Life and Welfare, King Gustaf V's and Queen Victoria Freemasons Foundation, AFA Insurance, Swedish Council for Working Life and Social Research, Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning, grant from the Swedish State under the Läkar Utbildnings Avtalet agreement, and grant from the Västra Götaland Region; Turkey: Metabolic Syndrome Society, AstraZeneca, Turkey, Sanofi Aventis, Turkey; United Arab Emirates (UAE): Sheikh Hamdan Bin Rashid Al Maktoum Award For Medical Sciences and Dubai Health Authority, Dubai UAE.

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