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Fruit and vegetable consumption, cardiovascular disease, and all-cause mortality in China

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Evidence about the response patterns of fruit and vegetable consumption with the risk of cardiovascular disease (CVD) and all-cause mortality was inconsistent. These associations were examined using a large-scale, population-based Chinese cohort comprising 100,728 participants. A food-frequency questionnaire was used to assess fruit and vegetable consumption. Outcomes were ascertained by interviewing individuals or their proxies and checking hospital records or death certificates. Cox proportional hazards regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). At the 736,668 person-years of follow-up, 3,677 CVD cases and 5,466 deaths were identified. The multivariable-adjusted HRs for CVD across increasing quartiles of total fruit and vegetable consumption were 1 (reference), 0.94 (95%CI=0.85–1.04), 0.89 (95%CI=0.80–0.98), and 0.85 (95% CI=0.77–0.95). Moreover, participants in the highest quartile displayed a 13% lower risk of all-cause mortality (HR=0.87; 95% CI=0.80–0.95). A nonlinear dose-response relation was found for CVD, without additional benefits beyond a consumption of 600 g d^{-1}, whereas the all-cause mortality risk decreased along with higher consumption, with a linear trend. These associations remained significant for fruit consumption but not for vegetable consumption. Our findings indicated that greater fruit and vegetable consumption was significantly associated with a lower risk of CVD and all-cause mortality. Increasing fruit and vegetable consumption, especially fruit, in the general population would prevent CVD and premature mortality.

fruit, vegetable, cardiovascular disease, mortality

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of diet-related death and disability worldwide. Among the world's 20 most populous countries, China had the highest age-standardized diet-related CVD mortality in 2017 (Afshin et al., 2019). The China National Nutrition Surveys (CNNS) reported that a low level of fruit and vegetable consumption contributed to the largest numbers of estimated cardiometabolic deaths in 2010–2012 (He et al., 2019). Average life expectancy loss of 1.73 years and 0.30 years among Chinese adults in 2013 were caused by inadequate fruit and vegetable intake, respectively (National Health Commission of China and Chinese Center for Disease Control and Prevention, 2017). Fruit and vegetable are abundant supply of dietary fiber, micronutrients, and bioactive components, including vitamins, minerals, polyphenols, carotenoids, and organosulfur compounds (The China Nutrition Society, 2016), which might play a relevant role in the development of CVD and its intermediate factors, such as serum lipids, blood pressure, and body weight (Bertoia et al., 2015; Tang et al., 2017; Zhao et al., 2017).

Until recently, the available data suggested that increased fruit and vegetable consumption had a protective effect against CVD and all-cause mortality (Aune et al., 2017; Wang et al., 2014). However, most studies were from Western countries, where dietary habits may differ substantially from China. Some domestic studies focused solely on investigating the frequencies of fruit and vegetable consumption or were restricted to local areas of China (Du et al., 2016; Yu et al., 2014; Zhang et al., 2011). The relations between greater fruit and vegetable intake and lower risk of CVD and premature death have also been inconsistent. Some studies reported that the associations were proportional, whereas other studies displayed threshold effects (Aune et al., 2017; Gan et al., 2015; Wang et al., 2014), which led to different recommendations for fruit and vegetable intake across countries.

Therefore, we aimed to investigate the associations of fruit and vegetable consumption, combined or separately, with the risk of CVD and all-cause mortality using a large-scale and population-based prospective cohort involving 15 provinces, the Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) study.

RESULTS

Baseline characteristics

Among 100,728 participants with an average age of 51.5 years, 59.8% were female (Table 1). The median intake of total fruit and vegetable, total fruit, and total vegetable were 450.0 g d^{-1} (interquartile range (IQR)=(271.4–571.4)), 50.0 g d^{-1} (IQR=(17.9–142.9)), and 350.0 g d^{-1} (IQR=(250.0–500.0)), respectively. Strikingly, 41.5% of individuals failed to meet the total fruit and vegetable consumption (≥400 g d^{-1}) recommended by the World Health Organization (WHO) at the baseline. Participants with a higher total fruit and vegetable intake were more likely to be men, well educated, and alcohol drinkers.

Fruit and vegetable consumption and risk of CVD and all-cause mortality

At the 736,668 person-years of follow-up (median follow-up =7.3 years; maximum follow-up=16.5 years), we ascertained 3,677 CVD events and 5,466 all-cause deaths. We found that higher total fruit and vegetable intake was inversely associated with the risk of CVD and all-cause mortality (Table 2). The multivariate hazard ratios (HRs) for CVD were 0.94 (95% confidence interval (CI)=0.85–1.04), 0.89 (95% CI=0.80–0.98), and 0.85 (95%CI=0.77–0.95) for the second to fourth quartile of total fruit and vegetable intake compared with the first quartile, respectively. Notably, each 200 g d^{-1} intake of total fruit and vegetable could reduce 5% lower risk of developing CVD (HR=0.95; 95%CI=0.92–0.98). Similar patterns of associations were observed for CVD mortality and stroke incidence (Table S1 in Supporting Information), whereas there was no significant association for coronary heart disease (CHD). For all-cause mortality, only the highest category of intake could bring the beneficial effect, with an HR of 0.87 (95%CI=0.80–0.95) (Table 2). The dose-response curve indicated a nonlinear relationship of total fruit and vegetable intake with CVD incidence, and that the estimated risks decreased with the elevated intake at the range of 0–600 g d^{-1}, with no further decrease at the intake exceeding 600 g d^{-1} (P-nonlinearity=0.0056) (Figure 1). There was no evidence for a nonlinear association between total fruit and vegetable intake and all-cause mortality (P-nonlinearity=0.3729).

If the observed associations are casual, our results suggested that 4.38% (95%CI=0.97–7.80) of CVD incidence and 6.40% (95%CI=1.02–11.78) of CVD deaths could be attributed to inadequate fruit and vegetable intake (Table S2 in Supporting Information). In 2017 in China, it is estimated that approximately 254,469 (95%CI=56,355–453,165) CVD events and 246,861 (95%CI=39,344–451,293) CVD deaths might be prevented by a total fruit and vegetable intake ≥400 g d^{-1}.

Table 1 Baseline characteristics of participants by quartiles of total fruit and vegetable consumption[a)]

Characteristic	Total	Quartiles of total fruit and vegetable consumption			
		Quartile 1 (<272 g d^{-1})	Quartile 2 (272–450 g d^{-1})	Quartile 3 (451–570 g d^{-1})	Quartile 4 (>570 g d^{-1})
No. of participants, *N*	100,728	25,407	25,344	24,451	25,526
Age (year)	51.5±12.2	52.8±13.1	51.5±12.4	52.0±11.6	49.9±11.4
Female, *N* (%)	60,232 (59.8)	15,803 (62.2)	15,376 (60.7)	14,377 (58.8)	14,676 (57.5)
High school or above, *N* (%)	13,583 (13.5)	2,092 (8.2)	2,875 (11.3)	3,299 (13.5)	5,317 (20.8)
Current smoker, *N* (%)	22,338 (22.2)	5,571 (22.0)	5,442 (21.5)	5,421 (22.2)	5,904 (23.1)
Alcohol drinker, *N* (%)	18,733 (18.6)	4,283 (16.9)	4,453 (17.6)	4,843 (19.8)	5,154 (20.2)
Family history of CVD, *N* (%)	10,098 (10.0)	2,260 (8.9)	2,558 (10.1)	2,430 (9.9)	2,850 (11.2)
Ideal physical activity, *N* (%)	67,560 (67.4)	15,581 (61.5)	17,618 (69.7)	17,327 (71.2)	17,034 (67.6)
Body mass index (kg m^{-2})	23.7±3.6	23.3±3.5	23.7±3.6	23.9±3.6	24.0±3.6
Hypertension, *N* (%)	33,762 (33.5)	8,219 (32.4)	8,644 (34.1)	8,779 (35.9)	8,120 (31.8)
Diabetes mellitus, *N* (%)	5,546 (5.8)	1,419 (5.9)	1,421 (6.0)	1,418 (6.2)	1,288 (5.3)
Dyslipidemia, *N* (%)	30,050 (31.3)	7,463 (31.1)	7,461 (30.9)	7,281 (31.3)	7,845 (32.1)
Ideal diet score, *N* (%)	48,808 (48.5)	11,292 (45.2)	12,687 (45.5)	11,809 (55.5)	13,020 (49.0)
Fruit intake (g d^{-1})	50.0 (17.9–142.9)	16.7 (3.3–33.3)	50.0 (28.6–100.0)	50.0 (18.0–142.9)	178.6 (71.4–214.3)
Vegetable intake (g d^{-1})	350.0 (250.0–500.0)	150.0 (100.0–200.0)	300.0 (250.0–300.0)	452.0 (400.0–500.0)	500.0 (493.0–600.0)

a) Data are mean±standard deviation or median (interquartile range) for continuous variables and numbers (percentages) for dichotomous variables.

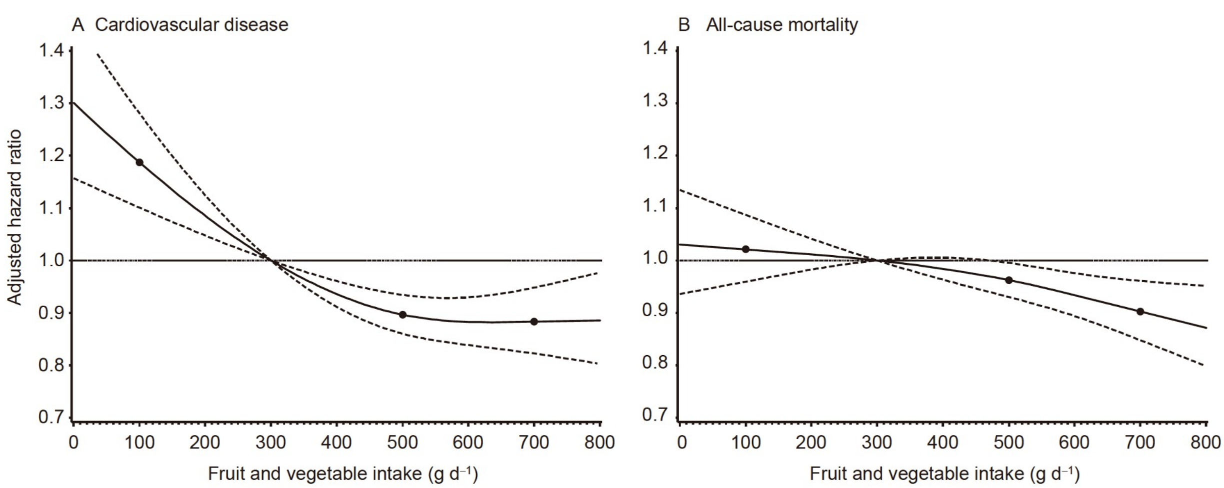

Figure 1 Dose-response relationships between total fruit and vegetable consumption and the risk of cardiovascular disease and all-cause mortality. A, Cardiovascular disease. B, All-cause mortality. Adjusted for age, sex, region, urbanization, educational level, smoking status, alcohol drinking status, family history of CVD, physical activity, body mass index, diet score, hypertension, diabetes mellitus, and dyslipidemia. Analysis was carried out after combining all three cohorts. Solid lines represented point estimates and dashed lines were 95% confidence intervals. Dots represented cutoff points for total fruit and vegetable consumption per day. *P* value for nonlinearity was 0.0056 for CVD, and 0.3729 for all-cause mortality.

In sensitivity analyses, results were not altered by omitting the incident CVD cases and deaths in the first year after baseline (Table S3 in Supporting Information). We also observed similar results when uniformly settled the baseline year at 2007 or excluded 1,449 non-Han Chinese population. No substantial changes occurred after adjusting for smoking, alcohol intake, or body mass index (BMI) as continuous variables. In addition, the findings were consistent across most subgroups, whereas there was heterogeneity in the association of total fruit and vegetable intake with the CVD risk by age groups (P=0.0041) (Figure 2) and with all-cause mortality by diabetes mellitus status (P=0.0171).

We repeated the analyses and investigated the associations of fruit and vegetable consumption separately. Increased total fruit intake was also related to a lower risk of CVD and all-cause mortality. Compared with the lowest quartile of total fruit intake, the multivariable-adjusted HRs for the highest quartile were 0.82 (95%CI=0.74–0.91) for CVD, 0.75 (95%CI=0.63–0.89) for CVD mortality, 0.81 (95% CI=0.74–0.89) for all-cause mortality, and 0.79 (95%

Table 2 Hazard ratios and 95% confidence intervals for cardiovascular disease and all-cause mortality across quartiles of fruit and vegetable consumption[a)]

Events	Quartiles of fruit and vegetable consumption				*P*-trend	Per portion increase
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
Total fruit and vegetable						
Median intake (IQR) (g d^{-1})	178.6 (127.4–250.0)	350.0 (316.7–404.0)	514.3 (500.0–535.7)	671.4 (600.0–753.6)		
CVD						
Cases/Person-years	862/156,258	906/174,303	948/183,622	961/216,132		
Incidence rate (per 100,000 person-years)	551.65	519.79	516.28	444.64		
HR (95%CI), Model 1	1.00	0.92 (0.84–1.01)	0.87 (0.79–0.96)	0.82 (0.74–0.91)	<0.0001	0.94 (0.91–0.97)
HR (95%CI), Model 2	1.00	0.95 (0.86–1.04)	0.91 (0.82–1.00)	0.85 (0.77–0.94)	0.0011	0.95 (0.92–0.98)
HR (95%CI), Model 3	1.00	0.94 (0.85–1.04)	0.89 (0.80–0.98)	0.85 (0.77–0.95)	0.0016	0.95 (0.92–0.98)
CVD mortality						
Cases/Person-years	378/157,332	361/175,631	381/185,382	363/218,323		
Mortality rate (per 100,000 person-years)	240.26	205.54	205.52	166.27		
HR (95%CI), Model 1	1.00	0.85 (0.73–0.99)	0.80 (0.69–0.93)	0.74 (0.63–0.86)	0.0001	0.91 (0.86–0.96)
HR (95%CI), Model 2	1.00	0.89 (0.77–1.04)	0.85 (0.73–0.99)	0.77 (0.66–0.91)	0.0018	0.92 (0.87–0.97)
HR (95%CI), Model 3	1.00	0.88 (0.75–1.02)	0.82 (0.70–0.96)	0.76 (0.65–0.90)	0.0011	0.92 (0.87–0.97)
All-cause mortality						
Cases/Person-years	1,359/157,332	1,335/175,631	1,433/185,382	1,339/218,323		
Mortality rate (per 100,000 person-years)	863.78	760.12	773	613.31		
HR (95%CI), Model 1	1.00	0.94 (0.87–1.02)	0.92 (0.85–1.00)	0.82 (0.75–0.89)	<0.0001	0.94 (0.91–0.96)
HR (95%CI), Model 2	1.00	0.99 (0.92–1.08)	0.99 (0.91–1.07)	0.85 (0.79–0.93)	0.0006	0.95 (0.92–0.98)
HR (95%CI), Model 3	1.00	0.99 (0.92–1.08)	1.00 (0.92–1.08)	0.87 (0.80–0.95)	0.0036	0.96 (0.93–0.98)
Total fruit						
Median intake (IQR) (g d^{-1})	6.9 (0.0–14.3)	35.7 (25.0–42.9)	71.4 (71.4–103.6)	214.0 (150.0–250.0)		
CVD						
Cases/Person-years	952/148,740	1,104/211,381	712/155,617	909/214,576		
Incidence rate (per 100,000 person-years)	640.04	522.28	457.53	423.63		
HR (95%CI), Model 1	1.00	0.92 (0.83–1.01)	0.86 (0.77–0.95)	0.79 (0.71–0.87)	<0.0001	0.91 (0.88–0.95)
HR (95%CI), Model 2	1.00	0.94 (0.85–1.03)	0.88 (0.80–0.98)	0.82 (0.74–0.91)	0.0002	0.92 (0.89–0.96)
HR (95%CI), Model 3	1.00	0.93 (0.84–1.02)	0.89 (0.80–0.99)	0.82 (0.74–0.91)	0.0003	0.93 (0.89–0.97)
CVD mortality						
Cases/Person-years	411/149,635	463/213,606	257/156,868	352/216,559		
Mortality rate (per 100,000 person-years)	274.67	216.75	163.83	162.54		
HR (95%CI), Model 1	1.00	0.87 (0.75–1.00)	0.75 (0.64–0.88)	0.73 (0.62–0.85)	0.0004	0.89 (0.84–0.95)
HR (95%CI), Model 2	1.00	0.89 (0.77–1.03)	0.79 (0.67–0.93)	0.76 (0.65–0.90)	0.0031	0.90 (0.85–0.97)
HR (95%CI), Model 3	1.00	0.88 (0.76–1.03)	0.79 (0.67–0.94)	0.75 (0.63–0.89)	0.0022	0.90 (0.84–0.97)
All-cause mortality						
Cases/Person-years	1,497/149,635	1,692/213,606	1,010/156,868	1,267/216,559		
Mortality rate (per 100,000 person-years)	1000.43	792.11	643.85	585.06		
HR (95%CI), Model 1	1.00	0.93 (0.86–1.01)	0.83 (0.77–0.91)	0.80 (0.73–0.87)	<0.0001	0.91 (0.88–0.94)
HR (95%CI), Model 2	1.00	0.95 (0.88–1.03)	0.86 (0.79–0.93)	0.81 (0.75–0.89)	<0.0001	0.92 (0.89–0.95)
HR (95%CI), Model 3	1.00	0.94 (0.86–1.02)	0.85 (0.78–0.93)	0.81 (0.74–0.89)	<0.0001	0.92 (0.89–0.95)
Total vegetable						
Median intake (IQR) (g d^{-1})	150.0 (100.0–150.0)	250.0 (250.0–300.0)	400.0 (400.0–450.0)	500.0 (500.0–525.0)		
CVD						
Cases/Person-years	718/142,279	968/192,093	844/173,025	1,147/222,918		
Incidence rate (per 100,000 person-years)	504.64	503.92	487.79	514.54		
HR (95%CI), Model 1	1.00	0.97 (0.88–1.07)	0.88 (0.80–0.98)	0.91 (0.83–1.00)	0.0185	0.98 (0.96–1.00)

(*To be continued on the next page*)

(*Continued*)

Events	Quartiles of fruit and vegetable consumption				*P*-trend	Per portion increase
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
HR (95%CI), Model 2	1.00	1.00 (0.90–1.10)	0.94 (0.85–1.05)	0.96 (0.87–1.06)	0.2524	0.99 (0.97–1.01)
HR (95%CI), Model 3	1.00	0.98 (0.88–1.08)	0.91 (0.81–1.01)	0.95 (0.86–1.05)	0.1890	0.99 (0.97–1.01)
CVD mortality						
Cases/Person-years	306/143,275	387/193,549	362/174,775	428/225,070		
Mortality rate (per 100,000 person-years)	213.58	199.95	207.12	190.16		
HR (95%CI), Model 1	1.00	0.95 (0.82–1.11)	0.87 (0.75–1.03)	0.85 (0.73–0.99)	0.0206	0.96 (0.93–0.99)
HR (95%CI), Model 2	1.00	0.99 (0.85–1.16)	0.95 (0.81–1.12)	0.91 (0.78–1.07)	0.1925	0.98 (0.95–1.01)
HR (95%CI), Model 3	1.00	0.99 (0.85–1.17)	0.93 (0.79–1.11)	0.90 (0.76–1.06)	0.1210	0.97 (0.94–1.01)
All-cause mortality						
Cases/Person-years	1,144/143,275	1,464/193,549	1,324/174,775	1,534/225,070		
Mortality rate (per 100,000 person-years)	798.47	756.40	757.55	681.57		
HR (95%CI), Model 1	1.00	1.00 (0.93–1.09)	0.96 (0.88–1.04)	0.90 (0.83–0.98)	0.0029	0.98 (0.96–0.99)
HR (95%CI), Model 2	1.00	1.06 (0.98–1.14)	1.06 (0.97–1.15)	0.97 (0.89–1.05)	0.3162	0.99 (0.98–1.01)
HR (95%CI), Model 3	1.00	1.08 (1.00–1.18)	1.07 (0.98–1.17)	0.99 (0.91–1.08)	0.5260	0.99 (0.98–1.01)

a) Cohorts-stratified Cox proportional hazards regression models were used. Model 1: Adjusted for age, sex, region, urbanization, educational level. Model 2: Model 1+smoking status, alcohol drinking status, family history of CVD, physical activity, body mass index, and diet score. Model 3: Model 2 +hypertension, diabetes mellitus, and dyslipidemia. Per portion was defined as 200 g d^{-1} for total fruit and vegetable intake and 100 g d^{-1} for total fruit or total vegetable intake. For total fruit intake, Model 2 and Model 3 were further adjusted for vegetable intake. For total vegetable intake, Model 2 and Model 3 were further adjusted for fruit intake.

CI=0.70–0.89) for stroke (Table 2 and Table S1 in Supporting Information). After adjustment for demographic factors, participants with the highest intake of total vegetable had a lower risk of CVD and all-cause mortality than those with the lowest intake, with an HR of 0.91 (95%CI=0.83–1.00) and 0.90 (95%CI=0.83–0.98), respectively. However, the effects were substantially attenuated in the fully adjusted models.

DISCUSSION

Using a large-scale and population-based Chinese prospective cohort, we provided the evidence that an increased total fruit and vegetable intake was associated with a decreased risk of CVD and all-cause mortality. This study identified the nonlinear dose-response relationship for CVD with a threshold of approximately 600 g d^{-1} of the total fruit and vegetable intake, above which no additional decrease in risk was observed. However, there was a monotonic decreasing trend for all-cause mortality. Furthermore, fruit consumption rather than vegetable might account for the beneficial effects.

Our findings are consistent with some previous studies in direction but there is a somewhat different magnitude of the benefits. A meta-analysis including 29 prospective cohort studies reported that each 200 g d^{-1} increment in total fruit and vegetable intake was associated with 8% (95%CI=5–10) and 10% (95%CI=7–13) lower risk of CVD and all-cause mortality, respectively. The continuous reductions of risks for both outcomes were observed along with the increasing total fruit and vegetable intake, with steeper inverse associations at lower levels of intake (Aune et al., 2017). Another meta-analysis of 16 prospective cohort studies revealed that the inverse relationship between total fruit and vegetable intake and all-cause mortality plateaued beyond intake of approximately 400 g d^{-1} (Wang et al., 2014). However, both meta-analyses described a significant interstudy heterogeneity for all-cause mortality, which seemed to be driven by a variation in causes of death from different populations. In addition, the Prospective Urban Rural Epidemiology study reported that risk reduction of all-cause mortality was the greatest at total fruit, vegetable, and legume intake of 375–500 g d^{-1} compared with that less than 125 g d^{-1} (Miller et al., 2017). Our study found a significant inverse relationship between total fruit and vegetable intake and CVD, with a threshold of approximately 600 g d^{-1} of intake and no extra decrease in risk reduction thereafter. A previous study hypothesized that the availability of nutrients and the digestibility of fruit and vegetable seemed to be responsible for the cutoff effects (Wang et al., 2014). The observed association might also be a result of the small number of subjects consuming high amounts of fruit or vegetable. We found only 4.7% participants who consumed more than 800 g of total fruit and vegetable daily, which may bias the results toward a nonlinear effect. Hence, more data is highly required before reaching firm conclusions. Furthermore, we failed to find significant protective effects of fruit and vegetable intake on CHD risk, which was identical to a previous Chinese study (Yu et al., 2014), but in contrast to some

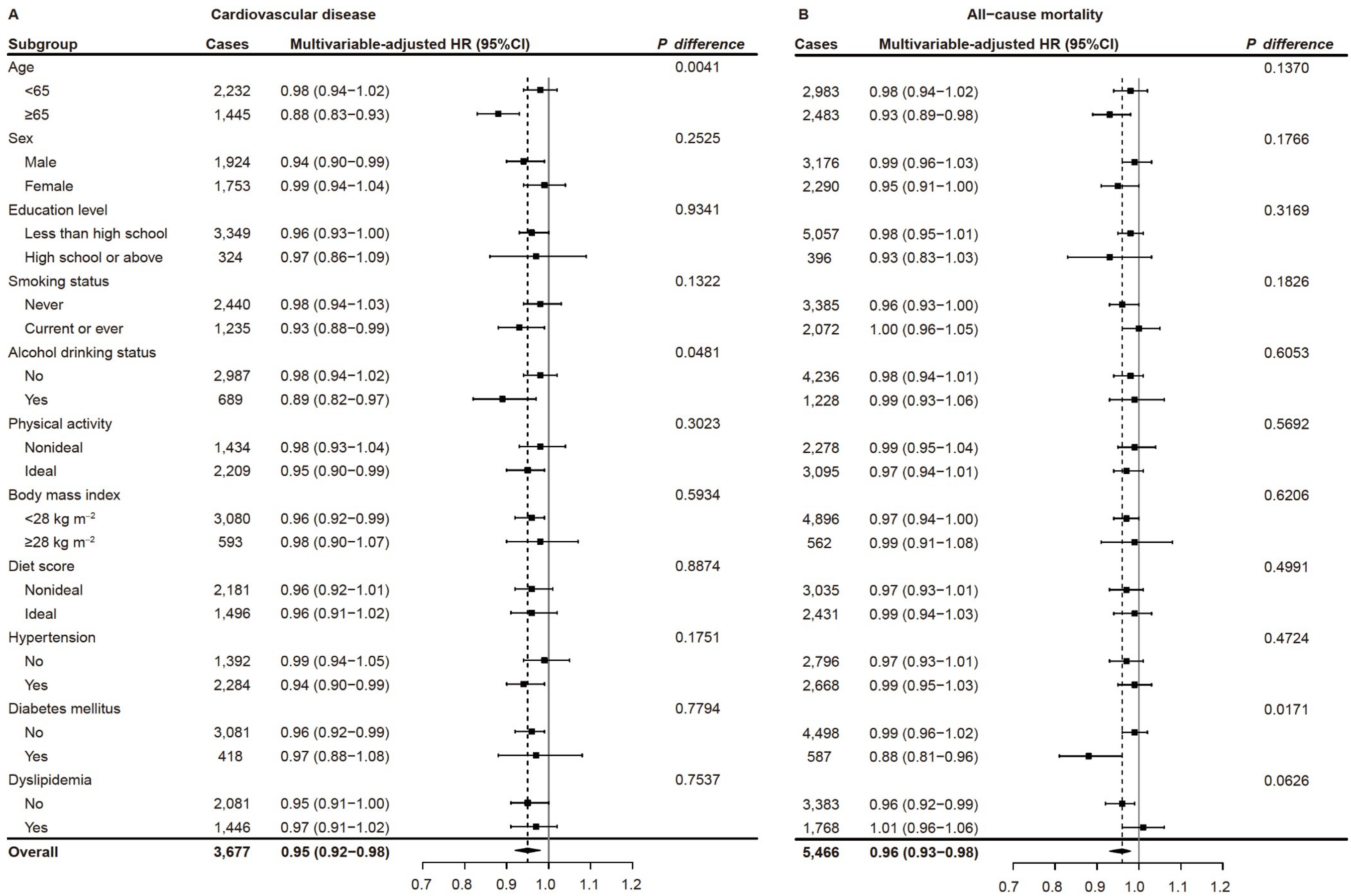

Figure 2 Multivariable-adjusted hazard ratios for cardiovascular disease and all-cause mortality with per 200 g d^{-1} of total fruit and vegetable consumption according to baseline characteristics. Cohorts-stratified Cox proportional hazards regression models were used. Adjusted for age, sex, region, urbanization, educational level, smoking status, alcohol drinking status, family history of CVD, physical activity, obesity, diet score, hypertension, diabetes mellitus, and dyslipidemia. The strata variable was not included in the model when stratifying by itself. The boxes represented hazard ratios and the horizontal lines represented 95% confidence intervals. The diamonds represented the overall hazard ratios and 95% confidence intervals.

Western studies (Bhupathiraju et al., 2013; Crowe et al., 2011). Inadequate numbers of CHD cases may account for the limited statistical power to detect significance.

We found that the preventative effects of fruit and vegetable on CVD risk were stronger among the elderly. Because an older age has been reported to increase oxidative stress (Finkel and Holbrook, 2000), the antioxidant properties in fruit and vegetable might be more beneficial to them (Alissa and Ferns, 2017). In addition, older people are more prone to take some multivitamin supplements, the components of which to some extent probably exaggerate the health effects of fruit and vegetable (Joshipura et al., 2001). Thus, further evaluation is needed. The magnitude of associations between total fruit and vegetable intake and all-cause mortality was obvious among the diabetic population, perhaps because individuals with diabetes mellitus tended to make lifestyle changes and compliance with treatment, which could lead to an improved survival and bias the results for all-cause mortality (Olofsson et al., 2017).

Similar to earlier studies, our results have indicated that fruit intake but not vegetable intake was linked to a lower risk of CVD and all-cause mortality (Crowe et al., 2011; Miller et al., 2017). It could be potentially explained by the following reasons. In traditional Chinese cuisine, fruit is typically consumed raw whereas vegetable may be eaten in various cooked ways. Diverse storage and preparation methods might influence the stability of some nutrients (Gil et al., 2006; Miller et al., 2017; Yu et al., 2014), such as ascorbic acid, riboflavin, and folate. There is some evidence suggesting a potential protective role of raw vegetable instead of cooked vegetable in preventing CVD and all-cause mortality (Miller et al., 2017). Furthermore, greater vegetable consumption is usually accompanied with a relatively higher salt intake, potentially resulting in adverse health effects (Du et al., 2014; Stefler et al., 2019). However, the data of exact salt intake were not available in this study. Therefore, further estimation should be conducted on raw and cooked vegetable consumption apart, taking salt intake into consideration.

Experimental studies in animals reported that fruit and vegetable extracts, such as the phenolics, triterpenoids, and ascorbic acid, have excellent antioxidant and antiinflammatory properties, by scavenging free radical, increasing the activities of antioxidant enzyme, reducing the production of reactive nitrogen species, and inhibiting the release of proinflammatory cytokine (Tang et al., 2017; Zhao et al., 2017; Zhu et al., 2018). Moreover, both observational and intervention studies in humans have also reported that an increase in fruit and vegetable intake was related to a reduction in some cardiovascular risk factors, such as blood pressure, waist circumference, total cholesterol, and low-density lipoprotein cholesterol (Liu et al., 2018; Mirmiran et al., 2015; Tang et al., 2017; Zhao et al., 2017).

In the past few years, healthy diets, especially promoting fruit and vegetable consumption, have been advocated by public health recommendations to prevent chronic diseases in China. However, the CNNS have reported that from 1982 to 2012, the average daily fruit consumption increased slightly (17.0 to 39.3 g d^{-1}) whereas the vegetable consumption decreased (330.0 to 248.0 g d^{-1}) among Chinese adults, which were far less than the dietary guideline recommendations (He et al., 2019). We estimated that approximately 6.40% of CVD deaths were preventable by consuming total fruit and vegetable ≥400 g d^{-1}. A recent nutrition trial from the United States also indicated that the DASH (Dietary Approaches to Stop Hypertension) diet, especially increased fruit and vegetable consumption, exerted positive effects on cardiovascular health (Juraschek et al., 2020). In particular, the relevant recommendations of dietary guidelines should give top priority to consuming more fruit, when considering the serious underintake among the Chinese population and higher health benefits of fruit compared with vegetable.

The strengths of this study include more than 100,000 participants who were enrolled from 15 provinces throughout China minimizing the regional differences of the effect, the long follow-up duration, and the high-quality data from standardized protocol with stringent quality control. Some limitations of our research must also be considered. First, total energy and nutrients intake could not be estimated and adjusted in our models, which might induce confounding bias. However, adjustment for their good proxy, including physical activity level and BMI, could reduce the bias. Second, the potentially beneficial effects of subtypes of fruit and vegetable could not be evaluated in this study (Aune et al., 2017; Bhupathiraju et al., 2013). Further research is needed. Third, participants with higher fruit and vegetable intake are liable to have specific social and behavioral characteristics, which may confound the observed associations. Although several variables were controlled in our multivariate analyses, we cannot rule out residual confounding completely (Aune et al., 2017). Finally, inevitable recall bias in self-reported dietary data and changes in dietary habits during long-term follow-up might result in misclassification.

CONCLUSIONS

Increased fruit and vegetable intake could reduce the risk of CVD and all-cause mortality. Our findings support public health recommendations and efforts to increase fruit and vegetable intake, especially fruit, in the general population to prevent CVD and premature mortality and further reduce the disease burden in China.

MATERIALS AND METHODS

Study population

The study population came from three prospective cohorts of the China-PAR project, including the China Multi-Center Collaborative Study of Cardiovascular Epidemiology (China MUCA) 1998, the International Collaborative Study of Cardiovascular Disease in Asia (InterASIA), and the Community Intervention of Metabolic Syndrome in China & Chinese Family Health Study (CIMIC). The China MUCA (1998) was conducted in 1998, and 15 clusters were selected using the cluster random sampling method, with an enrollment of approximately 1,000 participants at the age of 35 to 59 years in each cluster in China. The InterASIA was established from 2000 to 2001 and selected a nationally representative sample between the ages of 35 and 74 years using a four-stage stratified sampling method. The CIMIC was a prospective community-based cohort and 86,428 adults were recruited from three provinces (Shandong, Henan, and Jiangsu) with different economic development levels between 2007 and 2008. The first follow-up survey was conducted from 2007 to 2008 for both China MUCA (1998) and InterASIA cohorts. The last follow-up visits of all three cohorts were conducted from 2012 to 2015. Detailed description for the cohorts has been published elsewhere (Yang et al., 2016). The Institutional Review Board at Fuwai Hospital (Beijing, China) approved the study. A written informed consent was obtained from each participant before baseline and follow-up surveys.

A total of 113,448 participants completed the survey at enrollment, 105,263 of whom (92.8%) had successful follow-ups. We further excluded 4,535 participants who had missing values on fruit and vegetable consumption or had CVD or cancer at baseline, leaving 100,728 eligible participants in the final analysis (Figure S1 in Supporting Information).

Fruit and vegetable consumption assessment

The baseline survey of each cohort was conducted by well-trained interviewers using a standard protocol with stringent quality control. A standardized semiquantitative food-frequency questionnaire (FFQ) was used to assess food intake over the previous year at enrollment in each cohort. Participants were asked to report their consumption frequency (never, daily, weekly, monthly, or yearly) and average consumption amounts at each time for each food item, including fruit and vegetable. The reliability and validity of this FFQ were evaluated in a previous study (Zhao et al., 2010). Consumption frequencies and amounts were converted into an estimate of the daily consumption of each food. Legumes, potatoes, and other tubers were not considered as vegetable. Processed fruit and vegetable were also excluded, such as frozen, canned, dried, salted, pickled, or juices. The total fruit and vegetable intake was the sum intake of total fruit and total vegetable.

Outcomes ascertainment

At the follow-up surveys, diseases and vital information were acquired by interviewing participants or their proxies, confirmed locally by trained physicians, and then adjudicated by a study-wide endpoint assessment committee at Fuwai Hospital according to the hospital records or death certificates. The major outcomes were incident CVD and all-cause mortality. The incident CVD was defined as a combined endpoint of CHD, fatal or nonfatal stroke, or both combined. CHD included nonfatal acute myocardial infarction and CHD-related mortality. Stroke included ischemic stroke, hemorrhagic stroke, unspecified stroke, or death owing to a cerebrovascular event (Han et al., 2018; Yang et al., 2016).

Covariates assessment

Data on demographics (age, sex, living region, urbanization, and educational level), lifestyle factors (smoking status, alcohol drinking status, physical activity, and diet), family and personal medical history (family history of CVD, self-reported use of antihypertensive, antidiabetic, and lipid-lowering medications) at baseline were obtained from a standardized questionnaire. Physical activity was computed on the basis of average durations spent on various activities in the past year. Ideal physical activity was defined as a minimum of 150 min moderate aerobic activity or 75 min vigorous aerobic activity or an equivalent combination of both per week. Diet score was the number of ideal consumption of legumes (≥125 g d^{-1}), red meat (<75 g d^{-1}), fish (≥200 g per week), and tea (≥3 times per week) according to the recommendations of the Chinese dietary guideline and previous studies (The China Nutrition Society, 2016; Wang et al., 2020). Ideal diet was defined as a diet score of ≥2. Physical examinations were measured by standard protocol, including body weight, height, waist circumstance, and blood pressure. BMI was calculated by dividing measured weight (in kilograms) by the square of height (in meters). Hypertension was defined as a systolic blood pressure level of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg or current (within 2 weeks) use of antihypertensive drugs. Overnight fasting blood samples were collected to test serum glucose and lipids levels. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dL or currently under drug treatment for high blood glucose. Dyslipidemia was defined as currently taking cholesterol-lowing medicine or triglycerides of ≥200 mg/dL, total cholesterol of ≥240 mg/dL, low-density lipoprotein cholesterol of ≥160 mg/dL, or high-density lipoprotein cholesterol of <40 mg/dL.

Statistical analysis

Person-years of follow-up were calculated from the baseline examination to the date of the first diagnosis of CVD, death, or end of follow-up, whichever occurred first. For the primary analysis, participants were grouped into four categories (<272, 272–450, 451–570, and >570 g d^{-1}) according to quartiles of total fruit and vegetable consumption with the lowest quartile serving as the reference category.

The Cox proportional hazards regression model stratified on the study cohorts was used to estimate HRs (95%CIs) of CVD and all-cause mortality according to total fruit and vegetable intake. The Schoenfeld's residuals were used to test the proportional hazards assumption, with no evidence of violation (*P*>0.05). Models were sequentially adjusted for age (10-year intervals), sex, region (South or North China), urbanization, educational level (less than high school, high school or above) (model 1); plus smoking status (never smoker, former smoker, current smoker), alcohol drinking status (yes, no), family history of CVD (yes, no), physical activity (ideal, nonideal), BMI (<28 kg m^{-2}, ≥28 kg m^{-2}), and diet score (continuous) (model 2); plus hypertension (yes, no), diabetes mellitus (yes, no), and dyslipidemia (yes, no) (model 3). Potential nonlinear relationships of CVD and all-cause mortality associated with total fruit and vegetable intake were examined using restricted cubic splines with 4 knots (100 g d^{-1}, 300 g d^{-1} (reference), 500 g d^{-1}, 700 g d^{-1}). Furthermore, we calculated the population attributable fraction of CVD events and deaths owing to inadequate fruit and vegetable intake (<400 g d^{-1}) on the basis of WHO recommendations (WHO, 2020) using the formula $\left(\frac{\mathrm{Pe}[\mathrm{HR}-1]}{\mathrm{Pe}[\mathrm{HR}-1]+1}\right)$ proposed by Rockhill (Rockhill et al., 1998). In the abovementioned formula, Pe represents the prevalence of inadequate fruit and vegetable intake, which was calculated on the basis of data from the China Chronic Disease and Risk Factor Surveillance System (National Center for Chronic and Non-communicable Disease Control and Prevention, 2016). HR is the hazard ratio. The data on CVD incidence and mortality were derived from the Global Burden of Disease Study 2017 (Global Burden of Disease

Collaborative Network, 2020).

Sensitivity analyses were conducted to test the robustness of the results. We assessed the associations by (i) excluding first-year CVD events or deaths after baseline survey, (ii) setting the baseline year of 2007 (the baseline year of the CIMIC cohort) for all three cohorts (excluding participants died or diagnosed as having CVD or cancer before 2007), (iii) excluding 1,449 non-Han Chinese population, and (iv) adjusting for smoking pack year, daily alcohol intake (g ethanol per day), and BMI as continuous variables instead of categorical variables. To examine the potential effect modifications by baseline features, stratified analyses were performed to estimate the HRs within subgroups and compared by Z test (Altman and Bland, 2003).

We replicated main analyses separately for total fruit intake and total vegetable intake. In addition, we adjusted for vegetable intake for the analyses of fruit intake and vice versa.

SAS version 9.4 (SAS Institute Inc., USA) was used for data analyses. All statistical tests were two-sided, with $P<0.05$ being statistically significant.

Compliance and ethics *The author(s) declare that they have no conflict of interest. This study was approved by the institutional review board at Fuwai Hospital in Beijing, China.*

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SUPPORTING INFORMATION

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