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Associations of Combined Healthy Lifestyle Factors with Risks of Diabetes, Cardiovascular Disease, Cancer, and Mortality Among Adults with Prediabetes: Four Prospective Cohort Studies in China, the United Kingdom, and the United States

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ABSTRACT

Lifestyle modification is an effective measure for diabetes prevention in people with prediabetes, but its associations with the long-term risks of cardiovascular disease (CVD), cancer, and mortality remain largely uncertain. We aimed to investigate the associations of combined healthy lifestyle factors with these health outcomes among participants with prediabetes. The study included 121 254 people with prediabetes from four prospective cohorts: the Dongfeng-Tongji (DFTJ) cohort and Kailuan study, both from China; the UK Biobank; and the US National Health and Nutrition Examination Survey (NHANES; for mortality analysis only). We documented a total of 18 333 incident diabetes, 10 829 incident CVD, 6926 incident cancer, and 9877 deaths during follow-up. Combined healthy lifestyle scores (scored from 0 to 5) were constructed based on never smoking or quitting smoking for ≥ 10 years, low-to-moderate alcohol drinking, optimal physical activity, healthy diet, and optimal waist circumference. First, Cox proportional-hazards regression models were used to quantify the associations of combined lifestyle score with health outcomes in each cohort; then, multivariable-adjusted hazard ratios (HRs) were pooled via a random-effects model of meta-analysis. Compared with participants with the least healthy lifestyle (a score of 0–1), participants with the healthiest lifestyle (a score of 4–5) had significantly reduced risks of all outcomes. The HRs (95% confidence interval (CI)) were 0.57 (0.48–0.69) for diabetes, 0.67 (0.62–0.73) for CVD, 0.80 (0.73–0.88) for cancer, and 0.54 (0.42–0.70) for mortality. Significant associations were consistently found across subgroups of baseline demographic characteristics and metabolic health status. In conclusion, our pooled analyses of four cohorts from three countries reveal that greater adherence to a healthy lifestyle is associated with considerably lower risks of diabetes and its major complications among adults with prediabetes. These findings provide informative and compelling evidence for establishing clinical guidelines and public health policies.

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1. Introduction

Prediabetes, which is typically characterized as blood glucose or hemoglobin A$_{1c}$ (HbA$_{1c}$) levels above normal but below diabetes thresholds, has become a global epidemic [1,2]. The prevalence of prediabetes has been estimated to be 35.3%–38.1% among adults

in China, the United Kingdom, and the United States [3–5]. The prognosis of people with prediabetes generally worsens over time, and the lifetime risk of progression from prediabetes to diabetes is estimated to be around 70% [6–8]. Moreover, prediabetes has been demonstrated to be associated with markedly increased risk of diabetes and its complications, such as cardiovascular disease (CVD), cancer, and premature death [8,9], which cause a considerable disease burden [10]. On the other hand, reversion to normoglycemia has been found to be possible among adults with prediabetes with an annualized conversion rate of 5%–10% [8]; therefore, it is essential to identify modifiable risk factors that can be targeted to prevent or delay adverse health outcomes among people with prediabetes.

Lifestyle intervention is an effective measure for diabetes prevention in high-risk individuals with prediabetes, as demonstrated by a number of clinical trials, including the Da Qing Diabetes Prevention Outcome Study (DQDPOS) [11–13], the Finnish Diabetes Prevention Study (DPS) [14], and the US Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study (DPP/DPPOS) [15,16], along with recent meta-analyses of prior intervention studies [17,18]. However, it remains uncertain whether and to what extent healthy lifestyle factors are related to reduced risks of CVD, cancer, and mortality in people with prediabetes [19].

Such a study question is more likely to be answered by large cohort studies than by clinical trials, as the latter are usually designed to evaluate metabolic outcomes rather than other health outcomes and have a smaller sample size, insufficient statistical power, short follow-up duration, and unclear long-term adherence issue [19]. However, to the best of our knowledge, no cohort study has investigated the associations between combined lifestyle factors and multiple health outcomes (diabetes, CVD, cancer, and mortality) in adults with prediabetes. Taking advantage of comprehensive data from four large prospective cohort studies from China, the United Kingdom, and the United States, we aimed to fill these knowledge gaps and provide evidence for establishing clinical guidelines and public health policies.

2. Methods

2.1. Study design and participants

Participants with prevalent prediabetes were identified from two Chinese cohorts (i.e., the Dongfeng-Tongji (DFTJ) cohort and the Kailuan study), the UK Biobank study, and the US National Health and Nutrition Examination Survey (NHANES). The DFTJ cohort was launched in 2008 and recruited 27 009 retired employees from the Dongfeng Motor Corporation, Shiyan, China, in 2008–2010 [20]. Follow-ups were conducted every five years, with the additional enrollment of 14 120 new retirees in 2013. The Kailuan study was launched in 2006 and recruited 101 510 active and retired employees (aged 18 years or older) from the Kailuan (Group) Limited Liability Corporation, Tangshan, China, in 2006–2007 [21]. Follow-ups were conducted biennially, with additions of 25 337, 10 519, and 21 651 new employees enrolled in 2008–2009, 2010–2011, and 2012–2013, respectively. The UK Biobank recruited more than 500 000 participants (aged 37–73 years) from 22 assessment centers across England, Scotland, and Wales between 2006 and 2010 [22]. The NHANES is a national representative study of the US population with a complex, multistage probability sampling design. Detailed study designs and data collection have been previously described [23]. Data from the NHANES III (1988–1994) and continuous NHANES (1999–2014, each cycle was performed biennially) were used, and 61 202 non-pregnant adults aged 20 years or older were included. All cohort participants completed the questionnaire surveys, physical examinations, and blood biochemical tests. According to the latest criteria of the American Diabetes Association (ADA) [24], prediabetes was defined as a fasting plasma glucose (FPG) level of 5.6–6.9 mmol·L^{-1} (100–125 mg·dL^{-1}), or an HbA$_{1c}$ of 5.7%–6.4% (39–47 mmol·mol^{-1}), or a 2-h plasma glucose (PG) level of 7.8–11.0 mmol·L^{-1} (140–199 mg·dL^{-1}) in diabetes-free participants. Definitions of prediabetes in each cohort are detailed in Section S1 in Appendix A.

A total of 161 733 participants were diagnosed with prediabetes at enrollment (i.e., baseline) in the four cohorts. We excluded participants with prevalent CVD or cancer, or with missing information on death status, lifestyle factors, and covariates, leaving a total of 121 254 participants in the current analyses for incident CVD, incident cancer, and mortality (13 221 in the DFTJ cohort, 57 031 in the Kailuan study, 41 912 in the UK Biobank, and 9 090 in the US NHANES). In the analyses for incident diabetes, 566 participants from the DFTJ cohort and 6 470 participants from the Kailuan study were additionally excluded due to missing information on diabetes status during follow-up. In the US NHANES, information on incident disease outcomes was unavailable, and this cohort was used for mortality analysis only. These prospective cohort studies were approved by the Medical Ethics Committees of Tongji Medical College at the Huazhong University of Science and Technology (DFTJ cohort), the Kailuan General Hospital Ethics Committee (Kailuan study), the North West Multi-Centre Research Ethics Committee (UK Biobank), and the National Center for Health Statistics Research Ethics Review Board (US NHANES). All participants provided written informed consent. Detailed inclusion and exclusion procedures are provided in Section S1 and Fig. S1 in Appendix A.

2.2. Construction of combined healthy lifestyle scores at baseline

According to previous studies and evidence for preventing major noncommunicable diseases from the World Health Organization (WHO) [25–27], we constructed a combined healthy lifestyle score based on five major modifiable lifestyle factors: smoking, alcohol drinking, physical activity, diet, and obesity status. Healthy levels for smoking (never smoking or quitting smoking for ≥ 10 years) and alcohol drinking (low-to-moderate alcohol drinking defined as current drinking of no more than 14 g ethanol per day for women and no more than 28 g ethanol per day for men) were defined universally across four cohorts, while healthy levels for the other three factors were defined based on cohort-specific criteria. The procedures for collecting the five lifestyle factors are presented in Section S1, and definitions for healthy levels are elaborated in Table 1. For each of the five lifestyle factors, we assigned 1 point for a healthy level and 0 points otherwise. The healthy lifestyle score was the sum of five factors and ranged from 0 to 5, with higher scores indicating healthier lifestyles. Participants scoring 0–1 and 4–5 points were respectively merged to increase statistical power, since few people scored 0 or 5.

2.3. Ascertainment of clinical health outcomes

The primary outcomes were incident diabetes, CVD, cancer, and all-cause mortality. Incident diabetes was defined as a self-reported physician diagnosis of type 2 diabetes, or the use of anti-diabetic medications, or FPG ≥ 7.0 mmol·L^{-1} (126 mg·dL^{-1}), or HbA$_{1c}$ ≥ 6.5% (48 mmol·mol^{-1}), according to the ADA criteria in two Chinese cohorts [24], and ascertained according to the International Classification of Disease 10th Revisions (ICD-10) codes (E11) in the UK Biobank. Incident CVD, including ischemic heart disease (IHD; ICD-10 codes, I20–I25) and stroke (I60–I61 and I63–I64), and incident cancer (C00–C97) were also ascertained in two Chinese cohorts and the UK Biobank. Causes of death were

Table 1
Definitions of healthy lifestyle factors in different cohorts.

Factor	Healthy level	Unhealthy level
Smoking	• Never smoking or quitting smoking for ≥ 10 years	• Current smoking or quitting smoking for < 10 years
Alcohol drinking	• Women: 1–14 g ethanol per day; men: 1–28 g ethanol per day	• Women: none or > 14 g ethanol per day; men: none or > 28 g ethanol per day
Physical activity	• DFTJ cohort: weekly exercise ≥ 150 min • Kailuan study: weekly exercise ≥ 80 min • UK Biobank: top third of total physical activity • US NHANES 1999–2014: weekly ≥ 150 min of moderate-to-vigorous leisure-time physical activity • US NHANES 1988–1994: the top third of metabolic-equivalent-time-weighted frequency of leisure-time physical activity	• DFTJ cohort: weekly exercise < 150 min • Kailuan study: weekly exercise < 80 min • UK Biobank: bottom two-thirds of total physical activity • US NHANES 1999–2014: weekly < 150 min of moderate-to-vigorous leisure-time physical activity • US NHANES 1988–94: bottom two-thirds of metabolic-equivalent-time-weighted frequency of leisure-time physical activity
Diet	• DFTJ cohort: daily intakes of vegetable and fruit and no daily intakes of meat • Kailuan study: low or medium self-perceived salt intake • UK Biobank: meeting ≥ 5 items of more recent dietary recommendations for cardiovascular health[a] • US NHANES 1999–2014: top 40% of HEI-2010 score[b] • US NHANES 1988–1994: top 40% of HEI-1995 score[c]	• DFTJ cohort: no daily intakes of vegetable or fruit or daily intakes of meat • Kailuan study: high self-perceived salt intake • UK Biobank: meeting < 5 items of more recent dietary recommendations for cardiovascular health[a] • US NHANES 1999–2014: bottom 60% of HEI-2010 score[b] • US NHANES 1988–94: bottom 60% of HEI-1995 score[c]
Waist circumference	• DFTJ cohort and Kailuan study: waist circumference < 85 and 90 cm for women and men, respectively • UK Biobank and US NHANES: waist circumference < 80 cm and 94 cm for women and men, respectively	• DFTJ cohort and Kailuan study: waist circumference ≥ 85 and 90 cm for women and men, respectively • UK Biobank and US NHANES: waist circumference ≥ 80 and 94 cm for women and men, respectively

HEI: healthy eating index.

[a] Recommendation included fruit intake of ≥ 3 servings per day, vegetable intake of ≥ 3 servings per day, whole-grain intake of ≥ 3 servings per day, shell/fish intake of ≥ 2 servings per week, dairy intake of ≥ 2 servings per day, refined grain intake of ≤ 2 servings per day, processed meat intake of ≤ 1 serving per week, unprocessed meat intake of ≤ 2 servings per week, and no sugar-sweetened beverage intake.

[b] HEI-2010 score included intakes of total and whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, and empty calories.

[c] HEI-1995 score included intakes of grains, vegetables, fruits, milk, meat, total fat, saturated fat, cholesterol, sodium, and a variety of foods.

ascertained according to the ICD-10 codes in all four cohorts. Secondary outcomes included incident IHD, incident stroke, incident site-specific cancers, CVD mortality (I00–I99), and cancer mortality (C00–C97). To ensure sufficient statistical power, we only analyzed the top five site-specific cancers in each cohort. In the US NHANES, CVD mortality was unavailable, so mortality from heart disease was used. Details of outcome ascertainment in each cohort are provided in Section S1.

2.4. Statistical analyses

Baseline characteristics were described among the study population and across healthy lifestyle scores. In the US NHANES, analyses were performed according to the Centers for Disease Control and Prevention guidelines for analyses of the US NHANES dataset, accounting for complex survey designs using weighting methodology. In all four cohorts, continuous variables were presented as mean (standard deviation (SD)), and categorical variables were presented as n (%). Baseline characteristics were compared using analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables across healthy lifestyle scores, respectively.

Person-time was calculated from baseline to the date of events, deaths, or censoring dates, whichever came first. The administrative censoring date for the primary outcomes (i.e., incident diabetes, CVD, cancer, and all-cause mortality) was 31 December 2018 for the DFTJ cohort, 31 December 2019 for the Kailuan study, and 31 December 2015 for the US NHANES (mortality only). In the UK Biobank, the censoring dates varied for different outcomes because of the data availability issue: Vital status was obtained until 30 April 2020; incident CVD events were identified until 30 September 2020 in England, 31 August 2020 in Scotland, and 28 February 2018 in Wales; and incident diabetes and cancer cases were assessed until 31 March 2016 in England and Wales, and 31 October 2015 in Scotland. Details are depicted in Section S1.

Cox proportional-hazards regression models were applied to calculate multivariable-adjusted hazard ratios (HRs) and 95%

confidence intervals (CIs) for associations of individual and combined healthy lifestyle factors with outcomes of interest. Covariates included in the models were baseline age (continuous); sex; race/ethnicity; marital status; education; household income; employment status; prevalent hypertension; family histories of cancer, CVD, and diabetes; use of antihypertensive and lipid-lowering medications; continuous variables of FPG or HbA$_{1c}$; and total cholesterol (TC) levels. To test the linear trend, we treated the combined healthy lifestyle score as an ordinal variable in the Cox regression models. The definitions and availability of these covariates were slightly different in the four cohorts; details of the covariates assessment in each cohort are provided in Section S1. We also investigated the associations of each healthy lifestyle factor with all primary outcomes, and all five lifestyle factors were mutually adjusted in the models.

Subgroup analyses were conducted according to baseline age ($\geq 65/< 65$ years), sex (male/female), education level (less than high school, yes/no), normal weight status (i.e., 18.5–23.9 kg·m^{-2} in Chinese and 18.5–24.9 kg·m^{-2} in the US and UK cohorts, yes/no) [28], prevalent hypertension (yes/no), ideal blood lipid (blood TC < 5.2 mmol·L^{-1} without use of lipid-lowering medications, yes/no) [29], and glycemic status (FPG of 6.1–6.9 or 5.6–6.0 mmol·L^{-1} in Chinese cohorts, and HbA$_{1c}$ of 6.0%–6.4% or 5.7%–5.9% in the US and UK cohorts) [24]. Meta-regressions were used to estimate P values for the difference between subgroups. To minimize the probability of committing a type I error, we applied a Bonferroni correction for the significance level of $P < 0.0004 = 0.05/119$, which indicated a total of 119 tests in the subgroup analyses.

In addition, various sensitivity analyses were performed. First, we redefined the healthy level of alcohol drinking as no drinking or low-to-moderate alcohol consumption (i.e., healthy alcohol drinking as < 14 g per day of ethanol intake for females and < 28 g per day for males) [30]. Second, we excluded events occurring during the first two years of follow-up to minimize potential reverse causation. Third, we used multiple imputations in all cohorts to impute missing covariates in order to reduce the influence of non-responses. Fourth, we used the Fine and Gray method

to conduct competing risk analyses of death and generated sub-HRs [31]. Fifth, to explore the contribution of each healthy lifestyle factor, we omitted one factor each time from the score to reconstruct a new four-point combined healthy lifestyle score, and the participants were divided into three groups of 0–1, 2, and 3–4 points. In this case, we generated five new scores, and the omitted lifestyle factor was additionally adjusted in the analysis.

All analyses were performed by Stata 14 (StataCorp, College Station, USA). The HRs (95% CIs) from the four cohorts were pooled using a random-effects model of meta-analysis, which allowed between-study heterogeneity [32]. Heterogeneity across studies was assessed by the I^2 statistic (ranging from 0 to 100%), with a small value indicating less heterogeneity. Two-sided P values < 0.05 were considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Of the 121 254 participants, 70 252 were from China (the DFTJ cohort and Kailuan study), 41 912 were from the UK Biobank, and 9 090 were from the US NHANES. The mean age ranged between 49.4 (the US NHANES) and 62.6 years (the DFTJ cohort) at baseline across cohorts (Table 2). In the UK and US cohorts, the majority of participants (91.1% and 70.1%) were non-Hispanic white. The proportion with less than a high school education was higher in two Chinese cohorts (58.9% and 77.3%) than in the UK and US cohorts (20.4% and 16.8%). Given different definitions of five healthy lifestyle factors across cohorts, the proportions were not compared. Prevalent hypertension was higher in the UK Biobank (65.2%) and lower in the US NHANES (40.0%). Baseline TC levels were higher in the UK and US cohorts (5.9 and 5.5 mmol·L^{-1}) compared with the two Chinese cohorts (both 5.1 mmol·L^{-1}).

The distributions of the baseline characteristics in each cohort are presented in Tables S1–S4 in Appendix A. Compared with those with 0–1 healthy lifestyle factors, participants with an overall healthy lifestyle (4–5 healthy lifestyle factors) were more likely to be younger in the DFTJ cohort and the US NHANES, but older in the Kailuan study and the UK Biobank. They were less likely to be male in two Chinese cohorts and less likely to be female in the US and UK cohorts. In addition, they were more likely to have higher education levels and less likely to have prevalent hypertension across all four cohorts. The characteristics of the study participants included and excluded from the current analyses are compared in Table S5 in Appendix A, with the majority of the characteristics showing modest differences.

3.2. Associations of combined healthy lifestyle factors at baseline with morbidity and mortality

We ascertained 18 333 incident diabetes cases (820 567 person-years), 10 829 incident CVD cases (1 083 098 person-years), and 6 926 incident cancer cases (934 531 person-years) from the two Chinese cohorts and the UK Biobank study, and 9877 deaths (1 224 712 person-years) from the four cohorts in total. The pooled multivariable-adjusted HR (95% CI) comparing participants with a healthy lifestyle score of 4–5 versus 0–1 was 0.57 (0.48–0.69; I^2 = 83.4%; P = 0.002) for incident diabetes, 0.67 (0.62–0.73; I^2 = 0; P = 0.72) for incident CVD, 0.80 (0.73–0.88; I^2 = 0; P = 0.92) for incident cancer, and 0.54 (0.42–0.70; I^2 = 83.9%; P < 0.001) for all-cause mortality (Tables 3 and 4). The P values for the linear trend were all < 0.001, except for incident cancer in the DFTJ cohort (P for trend = 0.036).

In the secondary analyses, the pooled multivariable-adjusted HR (95% CI) comparing participants with a healthy lifestyle score of 4–5 versus 0–1 was 0.68 (0.60–0.78; I^2 = 32.9%; P = 0.23) for incident IHD, 0.66 (0.57–0.75; I^2 = 0; P = 0.47) for incident stroke, 0.47 (0.39–0.58; I^2 = 0; P = 0.56) for CVD mortality, and 0.52 (0.40–0.69; I^2 = 52.5%; P = 0.10) for cancer mortality (Table S6 in Appendix A). For the analysis of site-specific cancers, numbers (percentage) of the top five site-specific cancers in each cohort are shown in Table S7 in Appendix A. The pooled multivariable-adjusted HR (95% CI) comparing participants with a healthy lifestyle score of 4–5 versus 0–1 was significant for lung cancer (0.53 (0.28–0.99; I^2 = 79.7%; P = 0.007)) and colorectal cancer (0.64 (0.48–0.86; I^2 = 0; P = 0.55)), and was marginally significant for gastric cancer (0.66 (0.41–1.02; I^2 = 0; P = 0.53)) (Table S8 in Appendix A).

Table 2
Baseline characteristics of participants from different cohorts.

Baseline characteristics	DFTJ cohort	Kailuan study	UK Biobank	US NHANES[a]
Total number	13 221	57 031	41 912	9 090
Age (year)	62.6 (7.9)	52.4 (12.2)	59.1 (7.1)	49.4 (15.1)
Male	5 834 (44.1%)	47 157 (82.7%)	18 308 (43.7%)	5 224 (58.3%)
White	0	0	38 168 (91.1%)	3 710 (70.1%)
Currently not in a relationship	1 360 (10.3%)	1 427 (2.5%)	—	3 258 (31.6%)
Less than high school	7 791 (58.9%)	44 087 (77.3%)	8 557 (20.4%)	2 495 (16.8%)
Low household income[b]	—	—	9 951 (23.7%)	1 845 (12.8%)
Unemployed	—	—	2 989 (7.1%)	1 699 (16.2%)
Never smoking or quitting smoking for ≥10 years	10 313 (78.0%)	36 000 (63.1%)	32 571 (77.7%)	5 611 (54.8%)
Low-to-moderate alcohol drinking	1 784 (13.5%)	14 111 (24.7%)	16 459 (39.3%)	4 855 (53.4%)
Optimal physical activity	10 710 (81.0%)	8 485 (14.9%)	13 207 (31.5%)	2 360 (31.3%)
Healthy diet	3 691 (27.9%)	51 152 (89.7%)	9 058 (21.6%)	3 632 (40.4%)
Optimal waist circumference	8 950 (67.7%)	30 722 (53.9%)	11 270 (26.9%)	2 075 (24.3%)
Hypertension	7 029 (53.2%)	27 930 (49.0%)	27 324 (65.2%)	3 928 (40.0%)
Family history of cancer	474 (3.6%)	260 (0.5%)	12 747 (30.4%)	—
Family history of CVD	1 441 (10.9%)	2 609 (4.6%)	24 816 (59.2%)	1 186 (15.4%)
Family history of diabetes	770 (5.8%)	2 446 (4.3%)	11 209 (26.7%)	3 862 (42.8%)
Use of antihypertensive medications	3 263 (24.7%)	6 753 (11.8%)	11 087 (26.5%)	1 931 (18.0%)
Use of lipid-lowering medications	996 (7.5%)	325 (0.6%)	8 671 (20.7%)	889 (8.0%)
FPG (mmol·L^{-1})	5.9 (0.5)	6.0 (0.3)	—	—
HbA$_{1c}$	—	—	5.9% (0.2%)	5.5% (0.4%)
TC (mmol·L^{-1})	5.1 (1.0)	5.1 (1.3)	5.9 (1.2)	5.5 (1.1)

[a] In the US NHANES, all estimates accounted for complex survey designs. Continuous variables were presented as mean (SD), and categorical variables were presented as n (%).
[b] Low household income was defined as a household income < 18 000 GBP in the UK Biobank and a poverty-to-income ratio of ≤ 1 in the US NHANES.

Table 3
Associations of combined healthy lifestyle factors with risks of diabetes, CVD, and cancer in participants with prediabetes.

Outcomes	Number of healthy lifestyle factors				P value for trend
	0–1	2	3	4–5	
Incident diabetes					
DFTJ cohort					
Number of participants/person-years	1 267/8 948	3 803/27 509	5 259/38 537	2 326/16 606	
Age-adjusted rate of event (95% CI), per 1000 person-years	32.3 (28.5–36.1)	27.1 (25.2–29.0)	20.0 (18.6–21.3)	18.9 (16.8–21.0)	
Multivariable-adjusted HR (95% CI)	1.00	0.84 (0.73–0.96)	0.62 (0.54–0.71)	0.59 (0.50–0.69)	< 0.001
Kailuan study					
Number of participants/person-years	5 982/52 372	19 287/164 932	20 830/184 099	4 462/40 645	
Age-adjusted rate of event (95% CI), per 1000 person-years	26.8 (25.5–28.2)	25.2 (24.5–25.9)	18.2 (17.6–18.7)	16.5 (15.3–17.7)	
Multivariable-adjusted HR (95% CI)	1.00	0.94 (0.89–1.00)	0.71 (0.67–0.75)	0.65 (0.59–0.71)	< 0.001
UK Biobank					
Number of participants/person-years	14 777/100 170	14 662/100 490	8 912/61 488	3 561/24 771	
Age-adjusted rate of event (95% CI), per 1000 person-years	24.4 (23.4–25.4)	19.1 (18.3–20.0)	14.2 (13.2–15.1)	7.9 (6.8–9.0)	
Multivariable-adjusted HR (95% CI)	1.00	0.84 (0.79–0.90)	0.72 (0.67–0.78)	0.48 (0.42–0.56)	< 0.001
Pooled HR (95% CI), random-effects model	1.00	0.88 (0.81–0.96)	0.70 (0.65–0.74)	0.57 (0.48–0.69)	
I^2 (P value for heterogeneity)	—	71.8% (0.03)	46.4% (0.16)	83.4% (0.002)	
Incident CVD					
DFTJ cohort					
Number of participants/person-years	1 329/8 661	3 996/26 857	5 501/38 309	2 395/16 139	
Age-adjusted rate of event (95% CI), per 1000 person-years	44.1 (39.5–48.6)	38.6 (36.3–40.9)	30.3 (28.6–32.1)	29.2 (26.5–31.9)	
Multivariable-adjusted HR (95% CI)	1.00	0.89 (0.79–1.00)	0.71 (0.63–0.80)	0.70 (0.61–0.80)	< 0.001
Kailuan study					
Number of participants/person-years	6 672/65 623	21 791/207 282	23 634/223 161	4 934/48 031	
Age-adjusted rate of event (95% CI), per 1000 person-years	8.5 (7.8–9.3)	7.3 (6.9–7.7)	5.4 (5.0–5.7)	4.9 (4.2–5.5)	
Multivariable-adjusted HR (95% CI)	1.00	0.95 (0.86–1.05)	0.74 (0.67–0.83)	0.66 (0.57–0.77)	< 0.001
UK Biobank					
Number of participants/person-years	14 777/156 384	14 662/157 457	8 912/96 254	3 561/38 940	
Age-adjusted rate of event (95% CI), per 1000 person-years	11.4 (10.8–11.9)	9.3 (8.8–9.8)	8.4 (7.8–8.9)	6.5 (5.7–7.3)	
Multivariable-adjusted HR (95% CI)	1.00	0.83 (0.78–0.89)	0.78 (0.72–0.85)	0.65 (0.57–0.74)	< 0.001
Pooled HR (95% CI), random-effects model	1.00	0.88 (0.81–0.96)	0.75 (0.71–0.80)	0.67 (0.62–0.73)	
I^2 (P value for heterogeneity)	—	60.6% (0.08)	0 (0.42)	0 (0.72)	
Incident cancer					
DFTJ cohort					
Number of participants/person-years	1 329/9 749	3 996/29 808	5 501/41 228	2 395/17 401	
Age-adjusted rate of event (95% CI), per 1000 person-years	11.3 (9.2–13.4)	10.4 (9.2–11.5)	9.3 (8.4–10.3)	8.3 (6.9–9.6)	
Multivariable-adjusted HR (95% CI)	1.00	0.94 (0.76–1.17)	0.86 (0.70–1.07)	0.80 (0.62–0.98)	0.036
Kailuan study					
Number of participants/person-years	6 672/67 184	21 791/211 145	23 634/225 760	4 934/48 499	
Age-adjusted rate of event (95% CI), per 1000 person-years	4.8 (4.2–5.4)	4.2 (3.9–4.5)	3.6 (3.4–3.8)	3.3 (3.1–3.4)	
Multivariable-adjusted HR (95% CI)	1.00	0.96 (0.83–1.10)	0.87 (0.75–1.00)	0.77 (0.63–0.94)	< 0.001
UK Biobank					
Number of participants/person-years	14 777/99 909	14 662/99 485	8 912/60 322	3 561/24 041	
Age-adjusted rate of event (95% CI), per 1000 person-years	15.0 (14.2–15.8)	13.2 (12.5–13.9)	13.0 (12.1–13.8)	12.9 (11.5–14.3)	
Multivariable-adjusted HR (95% CI)	1.00	0.86 (0.79–0.92)	0.83 (0.76–0.91)	0.81 (0.71–0.91)	< 0.001
Pooled HR (95% CI), random-effects model	1.00	0.89 (0.83–0.95)	0.84 (0.79–0.91)	0.80 (0.73–0.88)	
I^2 (P value for heterogeneity)	—	5.8% (0.35)	0 (0.85)	0 (0.92)	

Heterogeneity across studies was assessed by I^2 statistic (ranging from 0 to 100%), with a small value indicating less heterogeneity.

Table 4
Associations of combined healthy lifestyle factors with all-cause mortality in participants with prediabetes.

Outcomes	Number of healthy lifestyle factors				P value for trend
	0–1	2	3	4–5	
DFTJ cohort					
Number of participants/person-years	1 329/10 021	3 996/30 584	5 501/42 227	2 395/17 807	
Age-adjusted rate of death (95% CI), per 1000 person-years	13.0 (10.7–15.2)	10.7 (9.5–11.8)	8.1 (7.2–8.9)	7.0 (5.7–8.2)	
Multivariable-adjusted HR (95% CI)	1.00	0.85 (0.69–1.04)	0.68 (0.55–0.83)	0.60 (0.47–0.78)	< 0.001
Kailuan study					
Number of participants/person-years	6 672/67 808	21 791/213 638	23 634/228 115	4 934/49 026	
Age-adjusted rate of death (95% CI), per 1000 person-years	9.4 (8.6–10.3)	8.6 (8.3–9.0)	7.5 (7.2–7.9)	6.2 (5.5–6.8)	
Multivariable-adjusted HR (95% CI)	1.00	1.00 (0.91–1.11)	0.90 (0.81–0.99)	0.71 (0.61–0.81)	< 0.001
UK Biobank					
Number of participants/person-years	14 777/160 950	14 662/160 756	8 912/97 754	3 561/39 159	
Age-adjusted rate of death (95% CI), per 1000 person-years	7.7 (7.3–8.1)	5.4 (5.0–5.8)	4.7 (4.3–5.1)	3.6 (3.0–4.1)	
Multivariable-adjusted HR (95% CI)	1.00	0.71 (0.65–0.78)	0.63 (0.57–0.71)	0.49 (0.41–0.58)	< 0.001
US NHANES[a]					
Number of participants/person-years	2 973/37 492	3 135/35 355	2 176/23 877	806/10 143	
Age-adjusted rate of death (95% CI), per 1000 person-years	21.5 (20.0–23.0)	15.8 (14.5–17.1)	13.8 (12.4–15.3)	10.3 (8.3–12.4)	
Multivariable-adjusted HR (95% CI)	1.00	0.77 (0.65–0.91)	0.67 (0.57–0.79)	0.39 (0.29–0.52)	< 0.001
Pooled HR (95% CI), random-effects model	1.00	0.83 (0.68–1.00)	0.72 (0.59–0.87)	0.54 (0.42–0.70)	
I^2 (P value for heterogeneity)	—	88.3% (<0.001)	88.0% (<0.001)	83.9% (<0.001)	

[a] In the US NHANES, all estimates accounted for complex survey designs. Heterogeneity across studies was assessed by I^2 statistic (ranging from 0 to 100%), with a small value indicating less heterogeneity.

3.3. Subgroup analyses and sensitivity analyses

The results were generally consistent in different subgroups according to demographic characteristics and metabolic health across the four cohorts (Tables S9 and S10 in Appendix A). In the sensitivity analyses of redefining the healthy level of alcohol drinking as no drinking or low-to-moderate alcohol consumption, excluding events occurring during the first two years of follow-up, using multiple imputations, and conducting competing risk analyses for death, the magnitudes of the associations between combined healthy lifestyle factors and morbidity and mortality remained largely unchanged in all four cohorts (Table S11 in Appendix A).

Most of the five individual lifestyle factors were associated with multiple outcomes (Table S12 in Appendix A). Low-to-moderate alcohol drinking, healthy diet, and optimal waist circumference were associated with 4%–44% lower risk of incident diabetes; all five lifestyle factors were associated with 5%–27% lower risk of incident CVD; never smoking or quitting smoking for ≥ 10 years, optimal physical activity, and optimal waist circumference were associated with 6%–23% lower risk of incident cancer; and never smoking or quitting smoking for ≥ 10 years, low-to-moderate alcohol drinking, and optimal physical activity were associated with 16%–38% lower risk of premature death. It was notable that, when one factor was omitted each time from the total score, the associations between the combined lifestyle factors and outcomes did not change materially (Table S13 in Appendix A).

4. Discussion

In these large cohorts of participants with prediabetes from China, the United Kingdom, and the United States, we found that individuals with 4–5 healthy lifestyle factors (characterized by never smoking or quitting smoking for ≥ 10 years, low-to-moderate alcohol drinking, optimal physical activity, healthy diet, and optimal waist circumference) had a 43% lower risk of developing diabetes, 33% lower risk of developing CVD, 20% lower risk of developing cancer, and 46% lower risk of death, compared with those with 0–1 healthy lifestyle factors. Our pooled analysis, which had a large sample size with greater statistical power than that of any single study, showed that these inverse associations were largely consistent across the four cohorts, irrespective of established risk factors such as age, sex, education level, and comorbidities. Various sensitivity analyses demonstrated the robustness of our findings.

Substantial evidence has shown that up to 70% of people with prediabetes eventually develop diabetes, and the annualized progression rate from prediabetes to diabetes ranges from 5% to 10%, with a similar proportion regressing to normoglycemia [6,8]. As an asymptomatic condition preceding the development of type 2 diabetes, prediabetes is an important period of early risk identification during which lifestyle modifications can be implemented in a timely manner. Moreover, lifestyle intervention is cost effective, feasible to implement in medical practice and health checkups, and more likely to have a longer sustainable effect compared with medication-based approaches in diabetes prevention among individuals with prediabetes [11,18,33–35]. Current clinical guidelines from the ADA recommend that people with prediabetes should adopt healthy behaviors for diabetes prevention [35], and a recent systematic review of 12 randomized clinical trials including 5238 people concluded that diet plus physical activity interventions reduced the risk of diabetes among people with prediabetes [17]. Nevertheless, few intervention studies have reported the impact of lifestyle interventions on CVD events and mortality outcomes among people with prediabetes, and the magnitude of the protective association remains unclear. The DQDPOS reported that six-year interventions (diet, exercise, or diet plus exercise) did not significantly reduce the risks of CVD and all-cause mortality among 577 adults with impaired glucose tolerance after 20 years of follow-up [13]; however, significant associations were observed for these outcomes after 30 years' follow-up [11]. The Finnish DPS reported no significant benefits from four-year interventions (diet plus exercise) among 522 adults in the ten-year follow-up [14]. The US DPP/DPPOS reported no effects of an intensive lifestyle intervention (diet, exercise, and weight reduction) on CVD events after three years' follow-up [15], or on mortality from all causes, CVD, and cancer over 21 years of follow-up among 3234 adults [16]. Moreover, no study has investigated the effects of lifestyle on incident cancer among people with prediabetes. Recent epidemiological analysis from the United Kingdom showed that cancer has overtaken vascular diseases as the leading cause of excess death in people with diabetes [36]; therefore, examining whether and to what extent lifestyle modification can reduce cancer incidence and mortality would provide valuable evidence for lowering excess death.

Limited sample size and/or events and insufficient statistical power are possible issues in such intervention studies; for example, the Finnish DPS only had 16 deaths and 111 CVD events (57 in the intervention group and 54 in the control group) among 522 participants. Therefore, evidence from large and well-characterized prospective cohort studies is urgently warranted.

Current evidence from the China Kadoorie Biobank (CKB) prospective cohort has shown that, in the whole Chinese population, combined healthy lifestyle factors are associated with 70%–80% lower risk of diabetes [37,38], 58% of major coronary events [39], 43% of liver cancer [40], and 68% of all-cause mortality [41]. However, those studies were conducted in the total population rather than specifically among people with prediabetes; thus, the effect sizes may differ. In addition, we have comprehensively reported the results for major chronic diseases and premature deaths. To the best of our knowledge, our study is the first cohort analysis to point out that adherence to combined healthy lifestyle factors is associated with substantially lower risk of diabetes, CVD, cancer, and mortality among over 120 000 participants with prediabetes from four prospective cohorts. Given that prediabetes is a global epidemic [1,2] and is a strong risk factor for diabetes and its complications [8,9], our findings highlight the importance of adopting a healthy lifestyle for the prevention of major chronic diseases and premature death in people with prediabetes, and provide strong evidence for establishing clinical guidelines and public health policies.

Our study has several strengths. Our analysis had a large sample size and long-term follow-up durations, which ensured sufficient statistical power to perform various subgroup and sensitivity analyses to test the robustness of our findings. In addition, all four cohort studies were well-characterized, and we used standardized variable definition and analysis approaches across cohorts. Although heterogeneities of the included studies were inevitable (e.g., active or retired employees in the Chinese cohort and whole populations in the UK and US cohorts), which is true for many other pooling projects or pooled analyses [42–44], the pooling approach is becoming increasingly used—or even preferred—in epidemiology. We consider our pooled approach to be a major advantage of our study, because the robust findings from four cohorts with different characteristics further emphasize the importance of a healthy lifestyle in reducing the risks of major adverse health outcomes and consolidate the generalizability of our findings.

Several limitations should be acknowledged as well. First, information on smoking, alcohol drinking, physical activity, and diet was self-reported, and measurement errors were inevitable. However, such misclassifications are more likely to be non-differential

and to lead to an underestimation of the associations because of the prospective design. Second, information on lifestyle factors was collected at baseline, and future studies with repeated measurements are warranted to investigate whether changes in lifestyle are associated with health outcomes. Third, we did not include other behavior factors and important environmental factors, such as sleep duration and occupational exposures, due to data availability issues and difficulties in data harmonization. Fourth, although we adjusted for multiple confounders in our analyses, unmeasured and residual confounding cannot be fully excluded. However, we deemed that the residual confounding would not substantially alter the robust associations observed in the study. Fifth, we defined incident CVD as incident ischemic heart disease and stroke; thus, further studies are warranted to investigate these associations in other types of CVD (e.g., heart failure and subdural hemorrhage) among people with prediabetes. Sixth, our results on the associations between combined healthy lifestyle factors and site-specific cancers should be interpreted with caution due to the limited number of events and probably inadequate statistical power. Seventh, information on other health outcomes, such as diabetes microvascular complications, was not available in our cohorts, and associations of combined lifestyle factors with those outcomes require further investigation. Finally, the two Chinese cohorts were not nationally representative; thus, more studies are needed in the Chinese population with representative samples.

5. Conclusions

In conclusion, our pooled analyses of four cohorts from three countries emphasized that adherence to combined healthy lifestyle factors was associated with remarkably lower risks of diabetes, CVD, cancer, and mortality among adults with prediabetes. Given that prediabetes comprises a large proportion of the whole population and is a strong risk factor for diabetes and its complications, our findings highlight the importance of adopting combined healthy lifestyle factors for the prevention of major chronic diseases and premature deaths in people with prediabetes, and provide compelling and valuable evidence for establishing clinical guidelines and public health policies.

Authors' contributions

Zhou-Zheng Tu, Qi Lu, Yan-Bo Zhang, Gang Liu, and An Pan conceived and designed the study. Zhou-Zheng Tu, Qi Lu, and Yan-Bo Zhang analyzed data. Zhou-Zheng Tu, Qi Lu, Yan-Bo Zhang, Zhe Shu, Jun-Xiang Chen, Xiong Ding, Xu Han, Shuo-Hua Chen, Mei-An He, Xiao-Min Zhang, Lie-Gang Liu, Tang-Chun Wu, Shou-Ling Wu, Gang Liu, and An Pan collected data. An Pan, Gang Liu, and Shou-Ling Wu are the guarantors of this work and, as such, had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the interpretation of the data and critical revision for important intellectual content and had final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved. The manuscript has been read and approved by all the authors. Each author believes that the manuscript represents honest work.

Compliance with ethics guidelines

Zhou-Zheng Tu, Qi Lu, Yan-Bo Zhang, Zhe Shu, Yu-Wei Lai, Meng-Nan Ma, Peng-Fei Xia, Ting-Ting Geng, Jun-Xiang Chen, Yue Li, Lin-Jing Wu, Jing Ouyang, Zhi Rong, Xiong Ding, Xu Han, Shuo-Hua Chen, Mei-An He, Xiao-Min Zhang, Lie-Gang Liu, Tang-Chun Wu, Shou-Ling Wu, Gang Liu, and An Pan declare that they have no conflict of interest or financial conflicts to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eng.2022.04.010.

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