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Complete List of Authors:	Zhang, Dudan; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Lin, Hongbo; Yinzhou District Center for Disease Control and Prevention TANG, Xun; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Shen, Peng; Yinzhou District Center for Disease Control and Prevention Si, Yaqin; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Liu, Xiaofei; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Xu, Zhe; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Wu, Jinguo; Wonders Information Co., Ltd. Zhang, Jingyi; Wonders Information Co., Ltd. Lu, Ping; Wonders Information Co., Ltd. GAO, Pei; Department of Epidemiology and Biostatistics, School of Public Health, Peking University
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Multimorbidity of cardiometabolic diseases: Prevalence and Risk of Mortality from One Million Chinese Adults in a Longitudinal Cohort Study

Dudan Zhang, BS[1]; Hongbo Lin, MD[2]; Xun Tang, PhD, MHS[1]; Peng Shen, MD[2]; Yaqin Si, BS[1]; Xiaofei Liu, BS[1]; Zhe Xu, MS[1]; Jinguo Wu, BS[3]; Jingyi Zhang, PhD[3]; Ping Lu, MS[3]; and Pei Gao, PhD[1#]

Affiliation

[1] Department of Epidemiology and Biostatistics, Peking University Health Science Center, Beijing 100191, China;

[2] Yinzhou District Center for Disease Control and Prevention, Ningbo 315100, China.

[3] Wonders Information Co., Ltd., Shanghai 201112, China.

[#] **Correspondence:**

Prof. Pei Gao, PhD (peigao@bjmu.edu.cn)

Department of Epidemiology and Biostatistics,

Peking University Health Science Center,

38 Xueyuan Road, Beijing 100191, China

Tel/Fax: +86-10-82805642

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Abstract

Objectives: Evolution of multimorbidity describes the continuum from healthy status, development of a single disease, and further progression to multimorbidity with additional diseases. We aim to investigate the evolution of cardiometabolic multimorbidity and their risk of mortality in a Chinese population.

Design: longitudinal cohort study: the CHinese Electronic health Records Research in Yinzhou (CHERRY) study during 5.43 million person-years follow-up (median 5.16 years).

Participants: Data from 1,038,704 adults (total 22,750 death) was analyzed.

Exposure: Cardiometabolic multimorbidity was defined as ever diagnosis of two or more following diseases: hypertension, diabetes and cardiovascular diseases (CVD).

Primary and secondary outcome measures: Age- and sex-adjusted hazard ratios (HRs) were calculated for all-cause mortality.

Results: Totally 105,209(10.1%) individuals changed their cardiometabolic disease status during follow-up. The prevalence of cardiometabolic multimorbidity increased from 2.41%(2.38%-2.44%) to 5.94%(5.90%-5.99%). Using baseline status of multimorbidity, the HRs were 1.37(1.33-1.42), 1.71(1.64-1.79) and 2.22(2.00-2.46) in patients with one, two or three diseases respectively. Among all combinations, patients with history of CVD only or diabetes and CVD were highest, i.e. 3.31(3.05-3.59) and 3.12(2.37-4.11) respectively, whereas patients with hypertension only had the lowest HR as 1.26(1.22, 1.30). In contrast, considering the longitudinal information, the HRs were 1.36(1.32-1.41), 2.03(1.96-2.10) and 2.16(2.05, 2.29) in patients with one, two or three diseases respectively.

Conclusions: The prevalence of patients having cardiometabolic comorbidity in a general population was more than doubled within 5 years, indicating rapid evolution

of cardiometabolic multimorbidity in Chinese. Among all combinations, history of CVD dominates the risk with mortality. A complementary strategy is needed in China.

Keywords: hypertension, diabetes, cardiovascular disease, multimorbidity, longitudinal

Strengths and limitations of this study

- This study is among the first to investigate the evolution of cardiometabolic multimorbidity and their risk of mortality in a general population under real-world circumstances in China.
- We used longitudinal design with continuous surveillance on cardiometabolic disease status in a general population to provide a better understanding of the etiological association and causality in addition to using the multimorbidity assessed only at baseline.
- The Chinese Electronic health Records Research in Yinzhou (CHERRY) study is a large, natural population-based, observational cohort study linking big data of integrated individual-level electronic health records (EHRs), with published protocol on *BMJ open* 2018; 8(2): e019698.
- Although the CHERRY study has a relatively large number of participants, it is a regional cohort located in a developed area of China and as such, will not be nationally representative.
- This study has relatively short period of follow-up where long-term effect of these cardiometabolic comorbidity will be further evaluated in the future.

INTRODUCTION

With the considerable improvement of medical intervention and healthcare management, the aging of population has become one of the major concerns in public health worldwide. Cardiometabolic comorbidity, defined herein as the co-existence of two or more of the following cardiometabolic disorders: hypertension, diabetes mellitus, cardiovascular disease (CVD), becomes progressively more common in the world and arises attention about their impacts on public health during past several years.[1-3] The prevalence of each individual disease is increasing rapidly along with significant changes in economic development and lifestyle in China.[4-7] Though a few studies evaluated the prevalence of multimorbidity based on cross-sectional design in China,[8-11] they have been limited by small sample size, judged as having a high risk of bias according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline, restriction to only elder population (>60 years), or included other chronic diseases (e.g. COPD or cancer) in the definition of multimorbidity. Moreover, multimorbidity is in fact a continuum, covering the transitions from healthy status, development of a single disease, and then progression to two or more multimorbidity with the addition of further diseases.[12] The term of "evolution of multimorbidity" was proposed to describe this whole process, which was generally required to be evaluated from a longitudinal perspective. There were limited studies in this case. However, none of them was conducted in Chinese populations.

On the other hand, many studies have shown that multimorbidity is associated with high risk of mortality.[13-15] Specifically, the Emerging Risk Factors Collaboration reported that mortality was similarly associated with a history of diabetes, stroke or MI and multiplicative mortality risk was observed for any combination of these conditions in Western population.[16] However, hypertension was not included in their evaluation. Time-varying exposure information to update multimorbidity status was also not available in their study. Longitudinal design with continuous surveillance on cardiometabolic disease status in a general population could provide a better understanding of the etiological association and causality in addition to using the multimorbidity assessed only at baseline.

Therefore, based on the Chinese Electronic Health Records Research in Yinzhou (CHERRY) study, which is a longitudinal cohort study and consisted of 1,038,704 adults and 22,750 deaths during 2010 through 2016, we aimed to provide reliable estimates about prevalence of cardiometabolic comorbidities, investigate the evolution of multimorbidity during follow-up, and assess their association with mortality in a Chinese population.

METHODS

Study Design

The CHERRY study is a longitudinal population-based ambispective cohort study for cardiovascular care and outcomes research by extracting individual participant data from regional health information system of Yinzhou, an eastern coastal area of China. Detailed description of this big data sources and cohort profile was published previously.[17] Specific data sources essential to this current study included: (1) the population census and registered health insurance database for individuals' general demographic characteristics; (2) health check databases including health checks from New Rural Cooperative Medical Scheme, elder people and adults with hypertension and diabetes; (3) inpatient and outpatient electronic medical records (EMRs); (4) disease surveillance and management database for capturing the incidence of CVD, hypertension, diabetes where cases were required to be reported for disease management by local general practitioners (GPs) once their diagnoses were confirmed; (5) death certificates database where attribution of death refers to the primary cause provided by cause-specific mortality.

All subjects were included in CHERRY study if they met all the following criteria: (1) over 18 years old on 1 January 2009; (2) have complete information on date of birth, sex, and a valid healthcare identifier; (3) have been living in Yinzhou for at least 6 months, and (4) have Chinese nationality. A total of 1,053,563 adults were originally enrolled in CHERRY study. In this analysis, we choose 1 January 2010 as the date of inception to bypass the integration and preliminary test period of the electronic health record (EHR) system and to allow for the

better coverage of the regional chronic disease management services. Overall, a total of 1,038,704 participants were included in current study after excluding subjects who died in 2009 or entered the system after 2016 (**eFigure 1**). Participants is generally continuously followed up in the health information system and imported into CHERRY study annually from the system. Complete follow-up data were available for participants through to 31th Dec 2016. This study was approved by the Peking University Institutional Review Board (IRB00001052-16011).

Cardiometabolic comorbidities and Outcome

Cardiometabolic comorbidity was defined as the presence of two or more following diagnosed disorders: hypertension, diabetes, or cardiovascular disease (CVD). We further categorized participants into the following 8 groups: (1) hypertension, (2) diabetes, (3) CVD, (4) hypertension and diabetes, (5) hypertension and CVD, (6) diabetes and CVD, (7) hypertension, diabetes and CVD, and (8) none of these diseases as the reference group. Diagnosis of these cardiometabolic diseases (and the date of diagnosis) were sought from multiple sources: diseases management database (primary care), EMRs (hospital care), and disease surveillance database (disease registry). Disease surveillance was considered as gold standard for the date of diagnosis for diseases. Details of the comprehensive health care services for chronic disease surveillance and management provided in this region was described previously.[17] Besides the baseline status of individuals' cardiometabolic diseases, longitudinal information of the exposure was also used. In this case, in order to evaluate the mortality association with a history of hypertension, diabetes, CVD and their cardiometabolic comorbidities, the change of cardiometabolic disease status occurred no more than 30 days before deaths was excluded, assuming that there was a direct connection between the change of cardiometabolic comorbidity status and mortality within the acute phase. The primary outcome was the all-cause mortality during the follow-up. Death was confirmed by death certificate in the health information system, which have been described previously.[18] Diseases and deaths were classified according to the International Classification of Diseases, Tenth Revision (ICD-10).

Statistical Analysis

Age- and sex- standardized prevalence and 95% CIs of cardiometabolic comorbidity at baseline and at the last visit were estimated in the overall population (and in population aged 40 years or older in the supplementary analysis) based on the distribution of the 2010 Chinese population census. 105,209 (10.1%) participants changed the cardiometabolic comorbidity status during follow-up. Numbers the corresponding percentages of participants who changed their cardiometabolic disease status within each 8 combination listed above were summarized. Poisson regression model adjusted to sex was used to calculate mortality rates adjusted to the age of 60 years. For the association of cardiometabolic multimorbidity with mortality, we firstly assessed the associations of the cardiometabolic comorbidity groups at baseline with risk of death from any cause. Furthermore, cardiometabolic comorbidity status was modelled as a time dependent exposure to enable updating of multimorbidity status during follow-up. The hazard ratios (HRs) were calculated using Cox proportional hazard regression models stratified by sex and adjusted for age in the primary analysis in overall population, population aged 40 years or older, and in subgroups of sex, age, location (urban / rural), status of smoking, and categories of body mass index. Finally, population attributable fractions (PAF) and 95% CI due to one, two or three cardiometabolic diseases were estimated by combining the proportional excess mortality (X_1, X_2, and X_3, where X=HR-1) and standard error in each category with the corresponding prevalence at baseline (P_1, P_2 and P_3).[19] The PAFs for one, two or ≥3 disorders are then P_1X_1/k, P_2X_2/k and P_3X_3/k, where $k=1 + P_1X_1 + P_2X2 + P_3X_3$. PAFs were calculated based on 1) the prevalence and HRs of cardiometabolic multimorbidity at baseline; 2) the prevalence at last visit and HRs using time-variant cardiometabolic multimorbidity status. All p values were two-tailed and were not adjusted for multiple testing. We judged p values less than 0.05 significant. We used Stata (version 14.0) for all data analyses.

RESULTS

The current cohort was established through the procedures listed in the **supplementary eFigure 1**. We began with 1.28 million permanent residents in Yinzhou, China with a valid personal identifier. After excluding subjects younger than 18 years old on or died before January 1 2010 and subjects entered the system after December 31 2016, we included overall 1,038,704 participants aged 18 years or older from CHERRY study in the current analyses. The baseline characteristics of the study participants were shown in **Table 1.** The mean (SD) age at baseline was 42.5 (14.8) and 51.4% were women. The mean (SD) of BMI was 22.5 (2.5) kg/m^2. According to Asian-specific cutoffs of BMI, 24.1% were overweight (23≤BMI<25 kg/m^2) and 13.9% were obese (BMI ≥25 kg/m^2).

Prevalence and Evolution of Cardiometabolic Comorbidity

At baseline, among total 1,038,704 subjects aged 18 years or older, 85,684 participants had a history of one diagnosed cardiometabolic disease, 22,871 participants had a history of two diseases, and 2,203 participants had 3 diseases respectively. The corresponding standardized prevalence were 9.32% (95% CI: 9.26%-9.37%), 2.57% (2.54%-2.60%) and 0.26% (0.25%-0.27%) respectively (**Table 2**). The estimated prevalence for the diagnosed cardiometabolic comorbidity was generally increased along with age and higher in women than men (**Figure 1**). Among the population aged 40 years or older, the standardized prevalence were 16.82% (16.72%-16.92%) for one disease, 4.69% (4.65%-4.75%) for two diseases and 0.47% (0.45%-0.49%) for three diseases respectively (**supplementary eTable 1)**. In the elderly population (aged 60 years or older), the corresponding prevalence increased to 31.90% (31.65%-32.14%), 10.41% (10.25%-10.57%) and 1.20% (1.14%-1.26%) respectively (**supplementary eTable 2)**.

A total of 105,209 out of 1,038,704 individuals (10.1%) in the study changed their cardiometabolic comorbidity status during median 5-year follow-up (**supplementary eTable 3**). The prevalence of cardiometabolic multimorbidity increased from 2.41% (2.38%-2.44%) to 5.94% (5.90%-5.99%) (**Figure 2**). The following four conditions with total 72,104 (68.5%) subjects lead all the transitions: 47,903 and 8,388 subjects developed

hypertension or diabetes from healthy condition respectively, 9,279 patients with hypertension and 6,534 patients with hypertension and diabetes further developed CVD. Among 927,946 subjects without any diagnosed cardiometabolic disease at baseline, 73,302 (7.9%) developed one or more cardiometabolic diseases. 47,903 (5.2%) subjects developed hypertension only. Among 85,684 subjects with only one disease at baseline, 24,041 (28.1%) developed additional cardiometabolic diseases. Among all 69,406 patients with hypertension at baseline, 12,711 (18.31%) patients had incidence of CVD during follow-up. Among all 14,127 patients with diabetes at baseline, 5,386 (38.13%) patients had incidence of CVD during follow-up. Finally, overall 7,865 (34.39%) out of 22,871 patients with two cardiometabolic diseases developed all three diagnosed diseases during follow-up. Patients with all three diseases increase from 2,203 at baseline to 18,547 by the end of the study (**supplementary eTable 3)**.

Association with mortality

There were total 22,750 deaths during 5.43 million person-years follow-up (median follow-up time, 5.16 years) in the study. Overall, the sex-adjusted all-cause mortality rate at the age of 60 years was 5.68 per 1000 person-years, with 6.50 in men and 4.91 in women. In the analysis using baseline status of cardiometabolic comorbidity, compared with the participants without any selected disease, the age- and sex-adjusted HRs (95% CIs) for mortality was 1.37 (1.33-1.42) in those with one disease, 1.71 (1.64-1.79) in those with two diseases, and 2.22 (2.00-2.46) in those with all three diseases (**Figure 3**). Among all the combinations of cardiometabolic comorbidity, patients with either history of CVD only or diabetes and CVD were highest, i.e. 3.31 (3.05-3.59) and 3.12 (2.37-4.11) respectively, whereas patients with hypertension only had lowest HR as 1.26 (1.22-1.30). HRs for cardiometabolic comorbidity were broadly similar in men vs. women, higher in younger participants (age<40 years), and higher in subjects living in urban areas (supplementary eTable 4). Sensitivity analysis for the analysis using baseline status excluding the initial 1 year of follow-up was broadly similar (**supplementary eTable 5**).

In contrast, considering the longitudinal information of the cardiometabolic comorbidity, compared with the participants without any selected disease at the last visit, the age- and sex-adjusted HRs (95% CIs) for mortality was broadly similar as 1.36 (1.32-1.41) in those with one disease, higher as 2.03 (1.96-2.10) in those with two diseases, and similar as 2.16 (2.05-2.29) in those with all three diseases (**Figure 3**). Though the pattern of HRs within each combination of comorbidity were broadly similar as the analysis using baseline status, the HR in patients with only hypertension reduced to 1.07 (1.03-1.10), whereas patients with history of CVD increased to 4.80 (4.55-5.07). Moreover, the HR in patients with hypertension and diabetes was attenuated to 1.30 (1.22-1.39), whereas patients with hypertension and history of CVD increased to 2.36 (2.27-2.45).

Population Attributable Fractions

Using the prevalence and HRs of cardiometabolic disease status at baseline, the population attributable fractions for all-cause mortality due to one cardiometabolic disease, two diseases and three diseases were 3.30% (2.95%-3.65%), 1.73% (1.56%-1.90%) and 0.30% (0.25%-0.36%) in the overall population aged 18 years or older (**Table 3**). In people aged 40 years old, PAF increased to 5.10% (4.52%-5.68%), 2.85% (2.56%-3.14%) and 0.50% (0.40%-0.59%) respectively. Using the prevalence at last visit and HRs using time-variant cardiometabolic disease status, PAFs due to one, two or three diseases were 4.17% (3.70%-4.63%), 4.36% (4.07%-4.65%) and 2.13% (1.92%-2.35%). The overall PAF increased from 5.34% (4.96%-5.72%) to 10.66% (10.11%-11.21%).

DISCUSSION

Our analyses of more than 1 million Chinese adults with 22,750 deaths occurred during follow-up in a longitudinal cohort has provided estimates of the prevalence of cardiometabolic comorbidity (i.e. hypertension, diabetes, and/or history of CVD) in a general population under real-world circumstances, investigate the evolution of cardiometabolic diseases in this population within 5-year of follow-up, and evaluated its association with risk of all-cause mortality. Each of our main findings has potential implications.

First, it was estimated that 12.2% of Chinese adults aged 18 years or older in a real-world general population have at least one diagnosed cardiometabolic disease and nearly 3% had cardiometabolic multimorbidity. Patients with hypertension dominates the patients with any selected disease. The prevalence of multimorbidity at baseline increased with age, which increased to 5.2% in the population aged 40 years or older and 11.6% in the population aged 60 years or older. Among all patients with any cardiometabolic disease, one in four had multimorbidity. This proportion was consistent in different age populations. Moreover, during the median of 5-year follow-up, the proportion of patients having multimorbidity was more than doubled. Strikingly, the proportion of patients had all three diseases in the original population were nine-fold than the baseline prevalence (0.2% to 1.8%). Nearly 60% of patients with both hypertension and diabetes at baseline had incidence of CVD during follow-up. Over 30% of patients having diabetes or 20% of patients with hypertension developed cardiometabolic comorbidity. These all indicated the surprisingly fast speed of the progression of cardiometabolic diseases.

There were limited publications on the epidemiology of multimorbidity in a general Chinese population. Most of them included other morbidities besides cardiometabolic diseases and only prevalence based on numbers of diseases were reported, which prevent us for the direct comparison. It is noted that the estimated prevalence of the single diagnosed disease was broadly consistent with those estimated from the national surveillance. For example, though the estimation of prevalence of diabetes in China reached 10.9% in 2013, the national prevalence of diagnosed diabetes was only 4%.[4] Because our population located in the developed area of China, our estimation of 3% is considered as consistent as the prevalence in this region is lower than the national estimation even in the traditional epidemiological survey.

Secondly, we observed about one-third increased risk in patients who had only 1 condition that we investigated at baseline, two-thirds higher risk in patients who had a combination of

any 2 diseases, and just over two-fold in patients who had all 3 conditions at baseline within 5-year of follow-up. Though these results appear to suggest that the association of hypertension, diabetes and cardiovascular disease with mortality were additive in this population, we found that there were significant heterogeneities within each combination of disease conditions. Patients with only hypertension at baseline has lowest HR of 1.26 and patients with CVD only at baseline had HR of 3.31. This pattern had been aggravated by applying longitudinal information of the cardiometabolic disease status. Patients with only hypertension reduced to 1.07 and patients with only CVD increased to 4.8. Within nearly 70,000 patients with hypertension at baseline, 15,000 of them developed additional cardiometabolic diseases and therefore changed the category of disease status. In addition, there were around 100,000 (10%) patients with hypertension at last in the study, nearly half of them were identified during follow-up, i.e. suggested that they were newly diagnosed. Therefore, using longitudinal information on disease status, patients with hypertension had lower HR than those using baseline status. In contrast, there were small number of patients (just over 2,000) at CVD only at baseline. Most of patients with history of CVD were accompanied by either diabetes or hypertension. Around 4,000 patients developed CVD during follow-up from healthy condition at baseline. We speculated that the increment of HR from 3.3 using baseline status to 4.8 using longitudinal data may be partly due to the relative short-term high risk after the first-ever CVD events. Similarly, we have also found the increased risk for patient group with hypertension and CVD from the analysis using baseline status to longitudinal definition of disease status.

In addition, regardless of the existence of other disease condition, history of CVD tends to dominate the risk especially within 5 years of follow-up. Among patients with any cardiometabolic diseases, patients with only history of CVD had highest risk, which may be short-term effect of newly diagnosed CVD. Alternatively, it may also indicate that patients with other cardiometabolic diseases, especially hypertension and/or diabetes, were likely to be more aware of their health condition. Moreover, within the group of cardiometabolic multimorbidity, only patients with hypertension and diabetes had significantly lower HR,

whereas other groups, i.e. all with CVD, were broadly similar, even in patients with all three conditions. In the results from the Emerging Risk Factor Collaboration (ERFC) of 91 cohort studies mainly from western population, they estimated that HR for mortality was about 2 in participants with one condition of cardiometabolic multimorbidity (type 2 diabetes, coronary heart diseases, and stroke) and the association was multiplicative.[16] They didn't include hypertension and used only baseline status of disease condition. We have seen that the broadly similar HR was found for patients with diabetes. Higher HR was estimated in our population for patients with CVD (stroke or MI) which may also be affected by the overall healthcare service across countries with different economic levels. The estimated HR for patients with CVD and diabetes (regardless of hypertension) was around 2.5, lower than the estimation from ERFC (around 3.5-4) but consistent with the Hispanic Established Population for the Epidemiological study of the Elderly (HR=2.4).[20] This may imply that the ethnic disparity could be one of the reasons. The present study also showed that cardiometabolic multimorbidity had more serious impact on population living in urban than in rural. It is important to take location difference in the consideration for making strategies to improve public health.

The strength and potential limitations of this investigation merit consideration. It is a large and comprehensive study under real-world circumstances. Especially, we took the longitudinal data of the cardiometabolic disease status to assess the prevalence and evolution of cardiometabolic multimorbidity during follow-up. However, the study also has several limitations. First, CHERRY study is based on a regional population in the developed area of China, which is not nationally representative. Secondly, this study has relatively short period of follow-up where long-term effect of these cardiometabolic comorbidity will be further evaluated in the future. Thirdly, the accurate time of onset for the diseases, especially hypertension and diabetes, were not available. We can only approximate this information by the first diagnose time of these chronic diseases. Finally, our laboratory data sources included the lipids measurements only in approximately 25% to 30% of the population, which prevent us from the model adjustment of conventional lipids risk factors. However, in the results

shown by ERFC, broadly similar HRs of cardiometabolic multimorbidity with mortality were observed after further adjustment of smoking, BMI, systolic blood pressure, high-density lipoprotein and total cholesterol, socioeconomic status and diet.

Conclusions

The prevalence of patients having cardiometabolic comorbidity in a general population was more than doubled within 5 years, indicating rapid evolution of cardiometabolic multimorbidity in Chinese. Among all combinations, history of CVD leads the risk with mortality. Our findings highlight the need for a complementary strategy for primary and secondary prevention of cardiometabolic diseases in China.

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Authors' contributions

DZ, XT, and PG drafted the manuscript. DZ, XT, PS, and PG conceived and designed the study. DZ, YS, and HL made substantial contributions to the study design. XT, XL, PS and HL are responsible for study coordination; XT, PS, JW, JZ and HL are responsible for data quality control; DZ, PL, and YS are responsible for data wrangling; XT, DZ, YS, XL, ZX and PG are responsible for data analysis. All authors contributed to the writing of the manuscript in an iterative manner, and have read and approved the final manuscript.

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Competing interests

None declared.

References

1. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition--multimorbidity. Jama 2012;307(23):2493-4. doi: 10.1001/jama.2012.5265 [published Online First: 2012/07/17]

2. Glynn LG. Multimorbidity: another key issue for cardiovascular medicine. Lancet 2009;374(9699):1421-2. doi: 10.1016/s0140-6736(09)61863-8 [published Online First: 2009/10/27]

3. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380(9836):37-43. doi: 10.1016/S0140-6736(12)60240-2

4. Wang L, Gao P, Zhang M, et al. Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. Jama 2017;317(24):2515-23. doi: 10.1001/jama.2017.7596

5. Wang W, Jiang B, Sun H, et al. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults. Circulation 2017;135(8):759-71. doi: 10.1161/circulationaha.116.025250 [published Online First: 2017/01/06]

6. Chen WW, Gao RL, Liu LS, et al. China cardiovascular diseases report 2015: a summary. Journal of geriatric cardiology : JGC 2017;14(1):1-10. doi: 10.11909/j.issn.1671-5411.2017.01.012 [published Online First: 2017/03/09]

7. Wu Y, Benjamin EJ, MacMahon S. Prevention and Control of Cardiovascular Disease in the Rapidly Changing Economy of China. Circulation 2016;133(24):2545-60. doi: 10.1161/circulationaha.115.008728 [published Online First: 2016/06/15]

8. Wang SB, D'Arcy C, Yu YQ, et al. Prevalence and patterns of multimorbidity in northeastern China: a cross-sectional study. Public Health 2015;129(11):1539-46. doi: 10.1016/j.puhe.2015.06.013

9. Wang HH, Wang JJ, Wong SY, et al. Epidemiology of multimorbidity in China and implications for the healthcare system: cross-sectional survey among 162,464 community

household residents in southern China. BMC Med 2014;12:188. doi: 10.1186/s12916-014-0188-0 [published Online First: 2014/10/24]

10. Hu X, Huang J, Lv Y, et al. Status of prevalence study on multimorbidity of chronic disease in China: systematic review. Geriatr Gerontol Int 2015;15(1):1-10. doi: 10.1111/ggi.12340

11. Gu J, Chao J, Chen W, et al. Multimorbidity in the community-dwelling elderly in urban China. Arch Gerontol Geriatr 2017;68:62-67. doi: 10.1016/j.archger.2016.09.001 [published Online First: 2016/09/23]

12. Ruel G, Levesque JF, Stocks N, et al. Understanding the evolution of multimorbidity: evidences from the North West Adelaide Health Longitudinal Study (NWAHS). PloS one 2014;9(5):e96291. doi: 10.1371/journal.pone.0096291 [published Online First: 2014/05/07]

13. Bragg F, Holmes MV, Iona A, et al. Association Between Diabetes and Cause-Specific Mortality in Rural and Urban Areas of China. Jama 2017;317(3):280-89. doi: 10.1001/jama.2016.19720

14. Yang G, Wang Y, Zeng Y, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2013;381(9882):1987-2015. doi: 10.1016/s0140-6736(13)61097-1 [published Online First: 2013/06/12]

15. Lewington S, Lacey B, Clarke R, et al. The Burden of Hypertension and Associated Risk for Cardiovascular Mortality in China. JAMA internal medicine 2016;176(4):524-32. doi: 10.1001/jamainternmed.2016.0190 [published Online First: 2016/03/15]

16. Emerging Risk Factors C, Di Angelantonio E, Kaptoge S, et al. Association of Cardiometabolic Multimorbidity With Mortality. JAMA 2015;314(1):52-60. doi: 10.1001/jama.2015.7008

17. Lin H, Tang X, Shen P, et al. Using big data to improve cardiovascular care and outcomes in China: a protocol for the CHinese Electronic health Records Research in Yinzhou (CHERRY) Study. BMJ Open 2018;8(2):e019698. doi: 10.1136/bmjopen-2017-019698 [published Online First: 2018/02/15]

18. Wang JB, Gu MJ, Shen P, et al. Body Mass Index and Mortality: A 10-Year Prospective Study in China. Scientific reports 2016;6:31609. doi: 10.1038/srep31609 [published Online First: 2016/08/23]

19. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388(10046):776-86. doi: 10.1016/s0140-6736(16)30175-1 [published Online First: 2016/07/18]

20. Otiniano ME, Du XL, Ottenbacher K, et al. The effect of diabetes combined with stroke on disability, self-rated health, and mortality in older Mexican Americans: results from the Hispanic EPESE. Arch Phys Med Rehabil 2003;84(5):725-30. [published Online First: 2003/05/09]

Table 1. Characteristics of participants at baseline.

	Participants ≥18 years	Participants ≥40 years
No. (%) of participants	1,038,704	545,632
Age (at baseline) mean (SD)	42.51 (14.84)	53.58 (11.63)
Body mass index (kg/m^2) mean (SD)	22.48 (2.53)	22.94 (2.66)
BMI (kg/m^2 Asian-specific cutoffs)		
<23 (Normal)	562,106 (62.04)	264,283 (53.65)
23-<25 (Overweight)	218,019 (24.06)	134,411 (27.29)
≥25 (Obese)	125,862 (13.89)	93,869 (19.06)
Gender No. (%)		
Male	504,525 (48.57)	275,382 (50.47)
Female	534,179 (51.43)	270,250 (49.53)
Location No. (%)		
Urban	316,900 (30.90)	168,208 (31.18)
Rural	708,642 (69.10)	371,311 (68.82)
Education levels No. (%)		
Primary school or lower	249,881 (29.11)	219,934 (45.78)
Middle school	547,890 (63.83)	248,425 (51.71)
College or higher	60,642 (7.06)	12,046 (2.51)
Smoking status (Current) No. (%)		
Never	726,241 (78.87)	388,223 (77.15)
Former smoker	20,524 (2.23)	17,678 (3.51)
Current smoker	174,084 (18.90)	97,328 (19.34)

Table 2. Standardized prevalence of cardiometabolic disease status at baseline.

	Overall (N=1,038,704)		Male (N=504,525)		Female (N=534,179)	
	No. of cases	**% (95% CI)**	**No. of cases**	**% (95% CI)**	**No. of cases**	**% (95% CI)**
One disease	85,684	9.32 (9.26-9.37)	40,883	8.64 (8.57-8.72)	44,801	10.01 (9.93-10.09)
HT	69,406	7.60 (7.55-7.65)	32,697	6.96 (6.89-7.02)	36,709	8.25 (8.18-8.33)
DM	14,127	1.49 (1.46-1.51)	6,992	1.43 (1.40-1.47)	7,135	1.54 (1.51-1.58)
CVD	2,151	0.23 (0.22-0.24)	1,194	0.25 (0.24-0.27)	957	0.21 (0.20-0.23)
Two diseases	22,871	2.57 (2.54-2.60)	10,349	2.24 (2.20-2.29)	12,522	2.90 (2.85-2.95)
HT+DM	11,073	1.26 (1.24-1.29)	4,722	1.03 (1.00-1.06)	6,351	1.50 (1.46-1.53)
HT+CVD	11,540	1.28 (1.25-1.30)	5,481	1.18 (1.15-1.21)	6,059	1.38 (1.34-1.41)
DM+CVD	258	0.03 (0.02-0.03)	146	0.03 (0.03-0.04)	112	0.03 (0.02-0.03)
Three diseases	2,203	0.26 (0.25-0.27)	841	0.19 (0.17-0.20)	1,362	0.33 (0.31-0.35)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Table 3. Population attributable fractions for cardiometabolic multimorbidity.

	Multimorbidity (% [95% CI])			
	1 disease	**2 diseases**	**≥3 diseases**	**Total**
Using the prevalence and HRs of cardiometabolic multimorbidity at baseline				
Participants ≥ 18years	3.30 (2.95-3.65)	1.73 (1.56-1.90)	0.30 (0.25-0.36)	5.34 (4.96-5.72)
Men	3.10 (2.65-3.54)	1.45 (1.24-1.65)	0.18 (0.12-0.24)	4.72 (4.24-5.21)
Women	3.68 (3.13-4.22)	2.11 (1.83-2.39)	0.44 (0.35-0.54)	6.23 (5.62-6.83)
Participants ≥ 40years	5.10 (4.52-5.68)	2.85 (2.56-3.14)	0.50 (0.40-0.59)	8.44 (7.82-9.07)
Participants ≥ 60years	6.11 (5.07-7.16)	4.60 (4.01-5.18)	0.96 (0.75-1.17)	11.67 (10.54-12.81)
Using the prevalence at last visit and HRs using time-variant cardiometabolic multimorbidity status				
Participants ≥ 18years	4.17 (3.70-4.63)	4.36 (4.07-4.65)	2.13 (1.92-2.35)	10.66 (10.11-11.21)
Men	4.19 (3.57-4.82)	4.14 (3.76-4.52)	1.69 (1.43-1.94)	10.02 (9.30-10.75)
Women	4.33 (3.62-5.05)	4.75 (4.30-5.20)	2.71 (2.35-3.07)	11.80 (10.95-12.64)
Participants ≥ 40years	5.92 (5.18-6.65)	6.95 (6.48-7.41)	3.49 (3.13-3.84)	16.35 (15.52-17.18)
Participants ≥ 60years	6.47 (5.36-7.58)	11.03 (10.19-11.88)	5.75 (5.09-6.41)	23.25 (21.98-24.53)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Figure legends

Figure 1. Prevalence of cardiometabolic disease according to age groups.

Note: HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Figure 2. Evolution of cardiometabolic disease status during follow-up.

Note: *Crude prevalence;HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Figure 3. Age- and sex-adjusted HRs (95%) for all-cause mortality by cardiometabolic disease status.

Note: HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

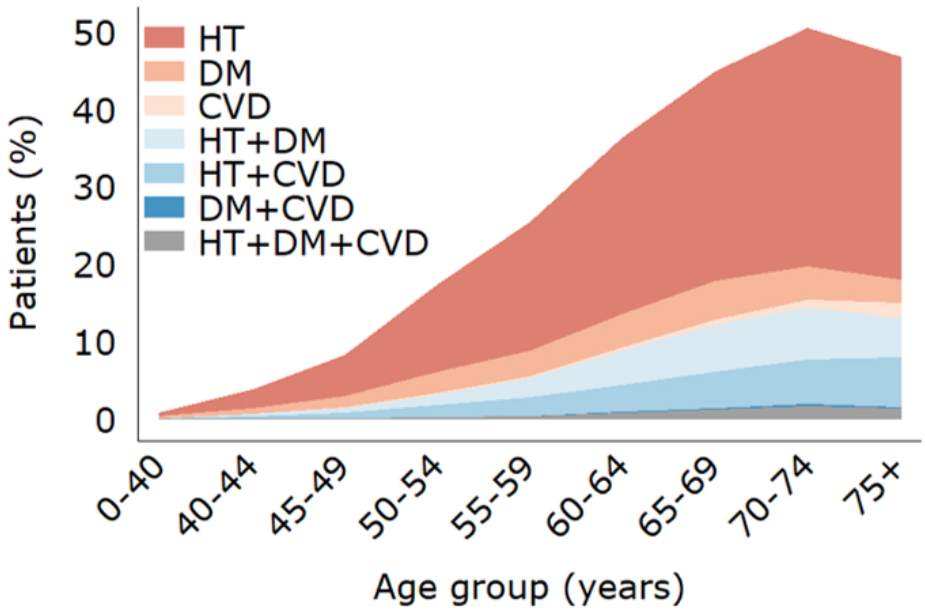


Figure 1. Prevalence of cardiometabolic disease according to age groups.

194x135mm (96 x 96 DPI)

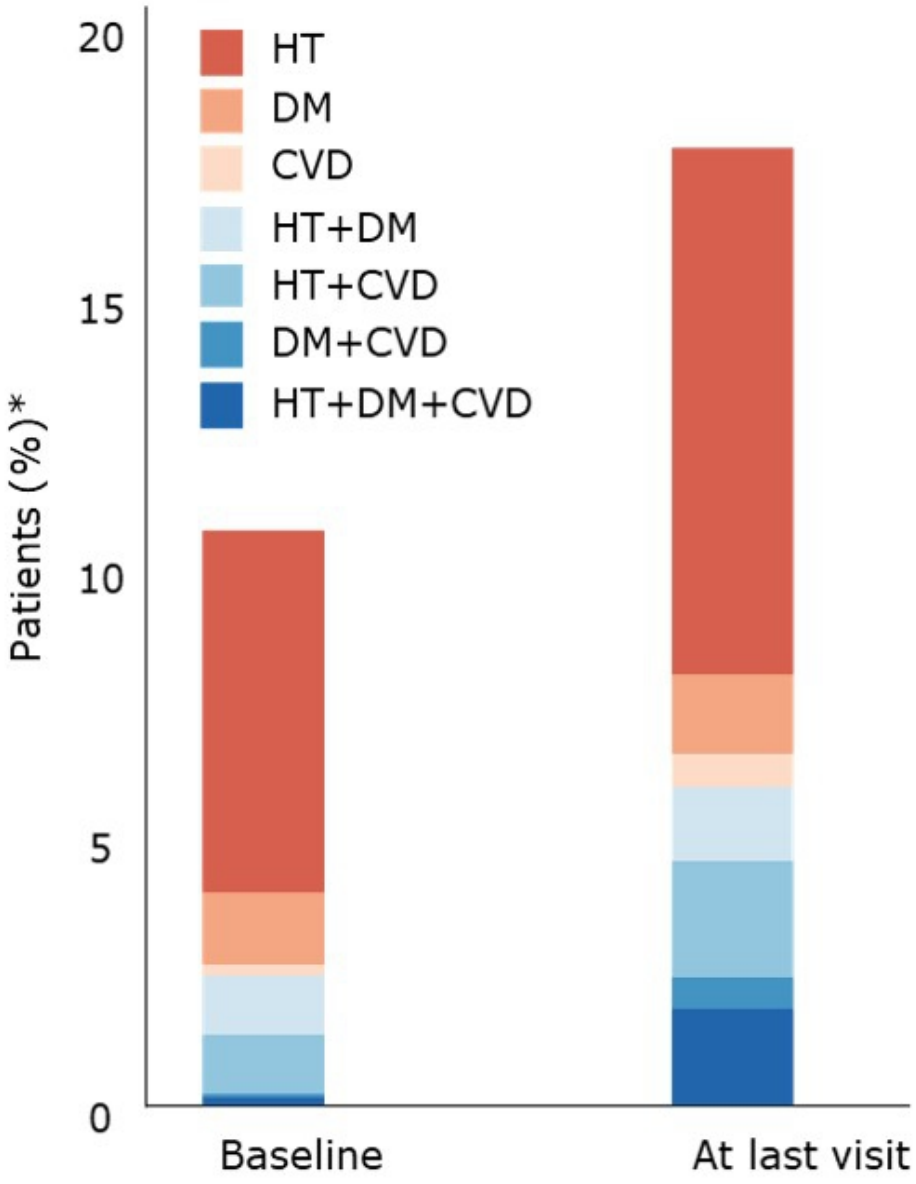


Figure 2. Evolution of cardiometabolic disease status during follow-up.

86x109mm (149 x 149 DPI)

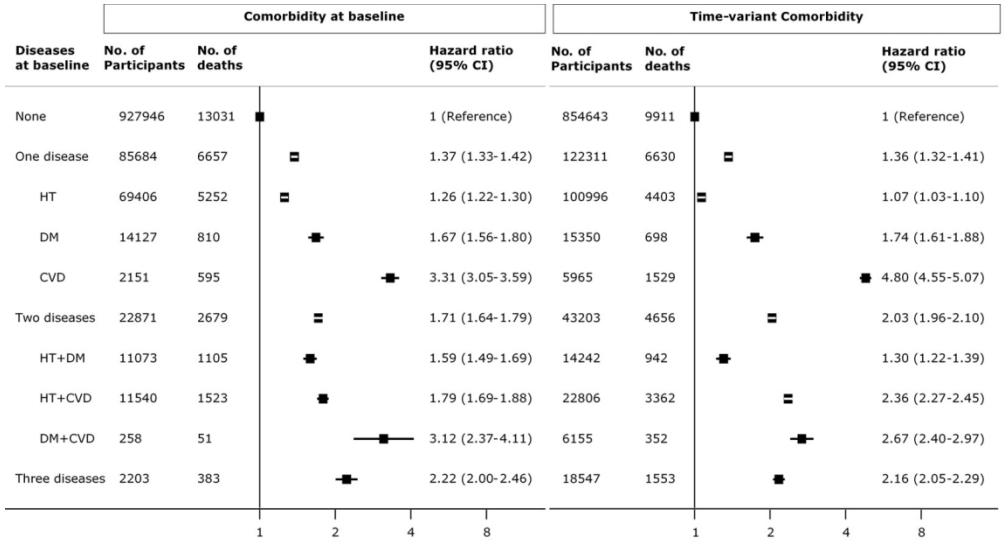


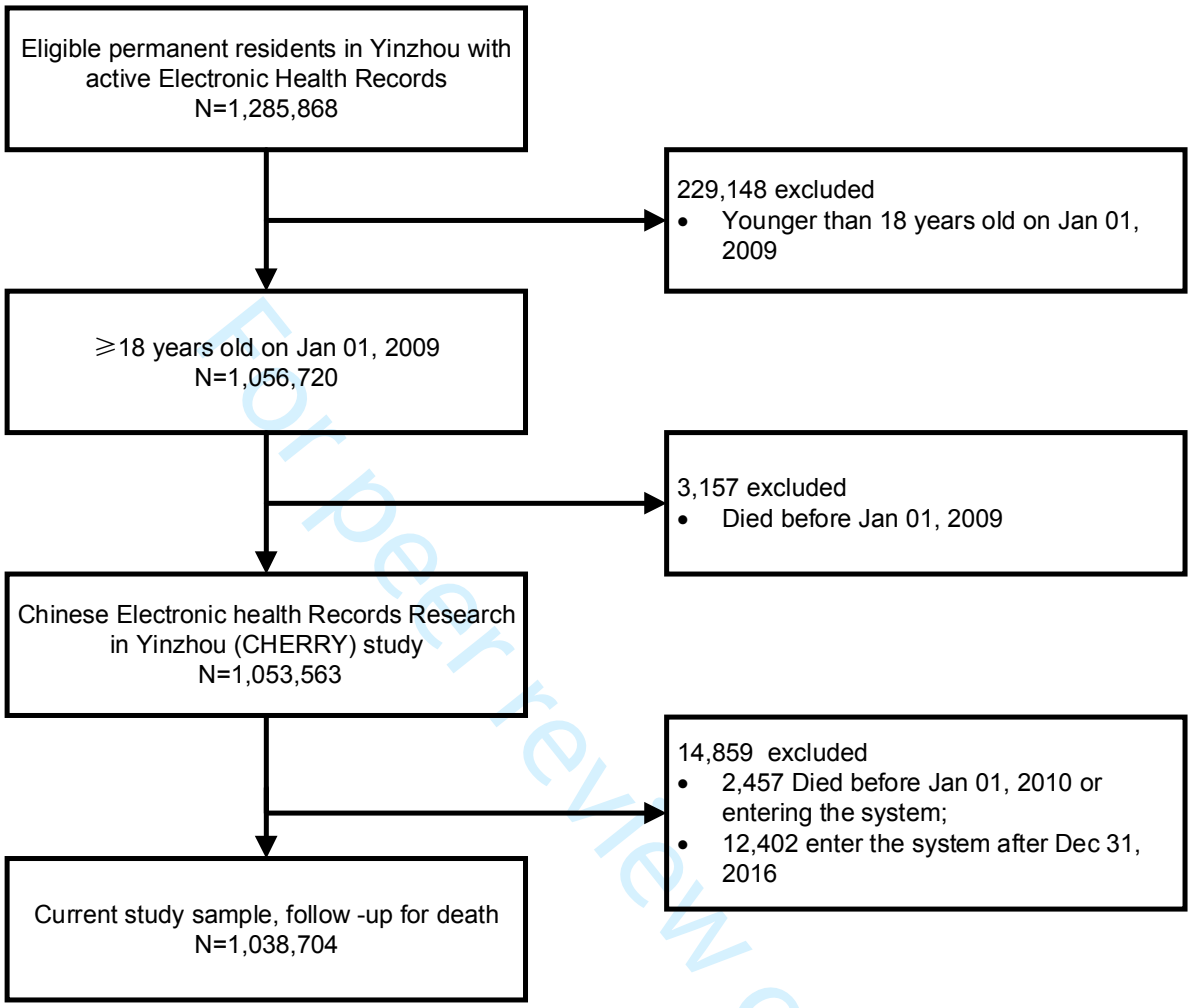
Figure 3. Age- and sex-adjusted HRs (95%) for all-cause mortality by cardiometabolic disease status.

291x169mm (143 x 143 DPI)

Supplementary Material

Multimorbidity of cardiometabolic diseases: Prevalence and Risk of Mortality from One Million Chinese Adults in a Longitudinal Cohort Study

eFigure 1. Flow chart of inclusion of participants in CHERRY study.



eTable 1. Standardized prevalence of cardiometabolic multimorbidity at baseline (age≥40 years).

	Overall (N=545,632)		Male (N=275,382)		Female (N=270,250)	
	No. of cases	**% (95% CI)**	**No. of cases**	**% (95% CI)**	**No. of cases**	**% (95% CI)**
One disease	82,589	16.82 (16.72-16.92)	39,133	15.54 (15.40-15.68)	43,456	18.11 (17.96-18.26)
HT	67,505	13.81 (13.71-13.90)	31,512	12.58 (12.46-12.71)	35,993	15.05 (14.91-15.19)
DM	13,041	2.59 (2.55-2.64)	6,481	2.50 (2.44-2.57)	6,560	2.68 (2.62-2.75)
CVD	2,043	0.42 (0.40-0.44)	1,140	0.45 (0.43-0.48)	903	0.38 (0.35-0.40)
Two diseases	22,405	4.69 (4.65-4.75)	10,065	4.09 (4.01-4.16)	12,340	5.31 (5.22-5.40)
HT+DM	10,966	2.33 (2.28-2.36)	4,656	1.90 (1.85-1.96)	6,310	2.76 (2.69-2.82)
HT+CVD	11,186	2.31 (2.27-2.36)	5,268	2.12 (2.07-2.18)	5,918	2.50 (2.44-2.57)
DM+CVD	253	0.05 (0.05-0.06)	141	0.06 (0.05-0.07)	112	0.05 (0.04-0.06)
Three diseases	2,185	0.47 (0.45-0.49)	828	0.34 (0.32-0.37)	1,357	0.60 (0.57-0.64)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

eTable 2. Standardized prevalence of cardiometabolic multimorbidity at baseline (age≥60 years).

	Overall (N=61,339)		Male (N=28,431)		Female (N=32,908)	
	No. of cases	**% (95% CI)**	**No. of cases**	**% (95% CI)**	**No. of cases**	**% (95% CI)**
One disease	45,083	31.90 (31.65-32.14)	21,351	30.06 (29.72-30.40)	23,732	33.66 (33.31-34.01)
HT	37,777	26.77 (26.54-27.00)	17,807	25.12 (24.80-25.44)	19,970	28.36 (28.02-28.70)
DM	5,833	4.12 (4.02-4.23)	2,733	3.84 (3.70-3.98)	3,100	4.39 (4.24-4.54)
CVD	1,473	1.00 (0.95-1.06)	811	1.10 (1.03-1.18)	662	0.91 (0.84-0.98)
Two diseases	14,597	10.41 (10.25-10.57)	6,448	9.11 (8.90-9.33)	8,149	11.65 (11.41-11.90)
HT+DM	7,398	5.32 (5.20-5.44)	3,057	4.33 (4.18-4.49)	4,341	6.26 (6.08-6.45)
HT+CVD	7,005	4.96 (4.84-5.07)	3,288	4.64 (4.48-4.79)	3,717	5.27 (5.10-5.44)
DM+CVD	194	0.13 (0.11-0.15)	103	0.14 (0.11-0.17)	91	0.12 (0.10-0.15)
Three diseases	1,659	1.20 (1.14-1.26)	632	0.89 (0.82-0.96)	1,027	1.49 (1.40-1.58)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

eTable 3. Evolution of cardiometabolic disease status during follow-up.

Number of disorders at baseline	Number of disorders at lase visit										
	None	**One disease**	HT	DM	CVD	**Two diseases**	HT+DM	HT+CVD	DM+CVD	**Three diseases**	**Total**
None	854,643 (92.1%)	60,668 (6.5%)	47,903 (5.2%)	8,388 (0.9%)	4,377 (0.5%)	9,931 (1.1%)	4,322 (0.5%)	2,798 (0.3%)	2,811 (0.30%)	2,704 (0.3%)	927,946 (89.3%)
One disease		61,643 (71.9%)				18,266 (21.3%)				5,775 (6.7%)	85,684 (8.2%)
HT			53,093 (76.5%)				3,602 (5.2%)	9,279 (13.4%)		3,432 (4.9%)	69,406 (6.7%)
DM				6,962 (49.3%)			1,779 (12.6%)		3,121 (22.1%)	2,265 (16.0%)	14,127 (1.4%)
CVD					1,588 (73.8%)			437 (20.3%)	48 (2.2%)	78 (3.6%)	2,151 (0.2%)
Two diseases						15,006 (65.6%)				7,865 (34.4%)	22,871 (2.2%)
HT+DM							4,539 (41.0%)			6,534 (59.0%)	11,073 (1.1%)
HT+CVD								10,292 (89.2%)		1,248 (10.8%)	11,540 (1.1%)
DM+CVD									175 (67.8%)	83 (32.2%)	258 (0.0%)
Three diseases										2,203	2,203 (0.2%)
Total	854,643 (82.3%)	122,311 (11.8%)	100,996 (9.7%)	15,350 (1.5%)	5,965 (0.6%)	43,203 (4.2%)	14,242 (1.4%)	22,806 (2.2%)	6,155 (0.6%)	18,547 (1.8%)	1,038,704

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

eTable 4. Age- and sex-adjusted HRs (95%) for all-cause mortality by cardiometabolic multimorbidity at baseline according to individuals' subgroups.

Subgroup		Number of disorders	n (total)	n (death)	HR (95% CI)
Gender	**Men**	0	452,452	7,390	1
		1	40,883	3,481	1.38 (1.32-1.43)
		2	10,349	1,316	1.68 (1.58-1.78)
		3	841	155	2.01 (1.71-2.36)
	Women	0	475,494	5,641	1
		1	44,801	3,176	1.39 (1.33-1.45)
		2	12,522	1,363	1.78 (1.67-1.88)
		3	1,362	228	2.44 (2.14-2.78)
Age groups	**<40 years**	0	489,493	391	1
		1	3,095	22	4.74 (3.06-7.33)
		≥2	484	2	1.91 (0.47-7.67)
	40-59 years	0	356,879	2,856	1
		1	37,506	538	1.10 (1.00-1.21)
		2	7,808	157	1.32 (1.13-1.56)
		3	526	16	1.87 (1.14-3.05)
	≥60 years	0	81,574	9,784	1
		1	45,083	6,097	1.22 (1.18-1.26)
		2	14,597	2,520	1.50 (1.44-1.57)
		3	1,659	367	1.91 (1.72-2.12)
BMI (kg/m2 Asian-specific cutoffs)	**<23 (Normal)**	0	520,434	6,971	1
		1	33,112	3,407	1.18 (1.13-1.23)
		2	7,879	1,223	1.47 (1.38-1.56)
		3	681	141	1.79 (1.51-2.11)
	23-<25 (Overweight)	0	187,405	2,617	1
		1	23,757	1,490	0.98 (0.92-1.04)
		2	6,294	588	1.16 (1.06-1.27)
		3	563	94	1.61 (1.31-1.98)
	≥25 (Obese)	0	89,870	1,430	1

		1	26,650	1,266	0.98 (0.90-1.05)
		2	8,404	705	1.32 (1.21-1.45)
		3	938	132	1.85 (1.55-2.21)
BMI (kg/m2)	**<25 (Normal)**	0	707,839	9,588	1
		1	56,869	4,897	1.10 (1.07-1.14)
		2	14,173	1,811	1.34 (1.28-1.41)
		3	1,244	235	1.71 (1.50-1.94)
	25-<30 (Overweight)	0	84,326	1,325	1
		1	23,991	1,132	0.97 (0.90-1.05)
		2	7,459	612	1.30 (1.18-1.43)
		3	804	115	1.86 (1.53-2.25)
	≥30 (Obese)	0	5,544	105	1
		1	2,659	134	1.01 (0.78-1.31)
		2	945	93	1.55 (1.17-2.06)
		3	134	17	1.79 (1.07-3.00)
Smoking status	**Current smoker**	0	162,325	1,762	1
		1	9,186	615	1.27 (1.15-1.39)
		2	2,411	236	1.50 (1.31-1.72)
		3	162	30	2.81 (1.96-4.04)
	Non-current smoker	0	650,393	10,132	1
		1	73,932	5,914	1.16 (1.12-1.20)
		2	20,400	2,433	1.45 (1.39-1.52)
		3	2,040	352	1.83 (1.64-2.03)
Region	**Rural**	0	638,725	10,421	1
		1	53,347	5,343	1.39 (1.35-1.44)
		2	15,043	2,015	1.57 (1.50-1.65)
		3	1,527	295	2.01 (1.79-2.25)
	Urban	0	279,407	2,521	1
		1	29,368	1,267	1.30 (1.21-1.39)
		2	7,468	628	2.06 (1.89-2.25)
		3	657	84	2.54 (2.04-3.15)

eTable 5. Age- and sex-adjusted HRs (95%) for all-cause mortality by cardiometabolic multimorbidity at baseline exclude follow-up less than one year.

Diseases at baseline	No. of Participants	No. of deaths	HR (95% CI)
None	916,681	10,941	1
One diseases	82,959	5,945	1.46 (1.42-1.51)
HT	67,560	4,767	1.35 (1.31-1.40)
DM	13,443	729	1.83 (1.70-1.97)
CVD	1,956	449	3.10 (2.82-3.40)
Two diseases	22,393	2,394	1.82 (1.74-1.90)
HT+DM	10,848	1,024	1.75 (1.64-1.87)
HT+CVD	11,317	1,331	1.85 (1.74-1.95)
DM+CVD	228	39	3.07 (2.24-4.20)
Three diseases	2,142	343	2.36 (2.12-2.63)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applied
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	5, eFigure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, eFigure 1
		(b) Give reasons for non-participation at each stage	eFigure 1
		(c) Consider use of a flow diagram	eFigure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	eFigure 1
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figure 3, eTable 4, 5
		(*b*) Report category boundaries when continuous variables were categorized	eTable 4, 5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	eTable 4, 5
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	3, 13-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	3, 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Multimorbidity of Cardiometabolic Diseases: Prevalence and Risk for Mortality from 1 Million Chinese Adults in a Longitudinal Cohort Study

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Complete List of Authors:	Zhang, Dudan; Department of Epidemiology and Biostatistics, School of Public Health, Peking University TANG, Xun; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Shen, Peng; Yinzhou District Center for Disease Control and Prevention Si, Yaqin; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Liu, Xiaofei; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Xu, Zhe; Department of Epidemiology and Biostatistics, School of Public Health, Peking University Wu, Jinguo; Wonders Information Co., Ltd. Zhang, Jingyi; Wonders Information Co., Ltd. Lu, Ping; Wonders Information Co., Ltd. Lin, Hongbo; Yinzhou District Center for Disease Control and Prevention GAO, Pei; Department of Epidemiology and Biostatistics, School of Public Health, Peking University; Key Laboratory of Molecular Cardiovascular Sciences (Peking University), Ministry of Education
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Multimorbidity of Cardiometabolic Diseases: Prevalence and Risk for Mortality from 1 Million Chinese Adults in a Longitudinal Cohort Study

Dudan Zhang, MS[1*]; Xun Tang, PhD, MHS[1*]; Peng Shen, MD[2]; Yaqin Si, MS[1]; Xiaofei Liu, BS[1]; Zhe Xu, MS[1]; Jinguo Wu, BS[3]; Jingyi Zhang, PhD[3]; Ping Lu, MS[3]; Hongbo Lin, MD[2]; and Pei Gao, PhD[1,4#]

* denotes equal contribution.

Affiliation

[1] Department of Epidemiology and Biostatistics, Peking University Health Science Center, Beijing 100191, China;

[2] Yinzhou District Center for Disease Control and Prevention, Ningbo 315100, China.

[3] Wonders Information Co., Ltd., Shanghai 201112, China.

[4] Key Laboratory of Molecular Cardiovascular Sciences (Peking University), Ministry of Education.

[#] **Correspondence:**

Prof. Pei Gao, PhD (peigao@bjmu.edu.cn)

Department of Epidemiology and Biostatistics,

Peking University Health Science Center,

38 Xueyuan Road, Beijing 100191, China

Tel/Fax: +86-10-82805642

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Abstract

Objectives: The evolution of multimorbidity describes the continuum from a healthy status to development of a single disease and further progression to multimorbidity with additional diseases. We investigated the evolution of cardiometabolic multimorbidity and risk for mortality in a Chinese population.

Design: Longitudinal cohort study using data from the CHinese Electronic health Records Research in Yinzhou (CHERRY) study, with 5.43 million person-years follow-up (median 5.16 years).

Participants: Data for 1,038,704 adults (total 22,750 deaths) were analyzed.

Exposure: Cardiometabolic multimorbidity was defined as ever being diagnosed with two or more of three diseases: hypertension, diabetes, and cardiovascular disease (CVD).

Primary and secondary outcome measures: Age- and sex-adjusted hazard ratios (HRs) were calculated for all-cause mortality.

Results: The cardiometabolic disease status of 105,209 (10.1%) individuals changed during follow-up. The prevalence of cardiometabolic multimorbidity increased from 2.41% (95% confidence interval [CI]: 2.38%–2.44%) to 5.94% (95% CI: 5.90%–5.99%). Baseline multimorbidity status showed the HR (95% CI) was 1.37 (1.33–1.42) in those with one disease, 1.71 (1.64–1.79) in those with two diseases, and 2.22 (2.00–2.46) in those with three diseases. The highest HRs were observed for CVD only (3.31, 95% CI: 3.05–3.59) or diabetes and CVD (3.12, 95% CI: 2.37–4.11). Those with hypertension only had the lowest HR (1.26, 95% CI: 1.22–1.30). Longitudinal data showed the HRs (95% CI) in patients with one, two, and three diseases were 1.36 (1.32–1.41), 2.03 (1.96–2.10), and 2.16 (2.05–2.29), respectively.

Conclusions: The prevalence of cardiometabolic multimorbidity in a general Chinese population more than doubled over 5 years, indicating rapid evolution of

cardiometabolic multimorbidity. A history of CVD dominates the risk for mortality. A complementary strategy for primary and secondary prevention of cardiometabolic diseases is needed in China.

Keywords: hypertension, diabetes, cardiovascular disease, multimorbidity, longitudinal

Strengths and limitations of this study

- This study is among the first to investigate the evolution of cardiometabolic multimorbidity and risk for mortality in a general population in China.
- We used a longitudinal design with continuous surveillance of cardiometabolic disease status to provide a better understanding of etiological associations and causality, in addition to using multimorbidity assessed only at baseline.
- The Chinese Electronic health Records Research in Yinzhou (CHERRY) study is a large-scale natural population-based observational cohort study linking large data from integrated individual-level electronic health records, the study protocol of which was published in *BMJ Open* 2018; 8(2): e019698.
- The CHERRY study involves a regional cohort located in a developed area of China, and is therefore not nationally representative.
- This study had relatively short follow-up period.

INTRODUCTION

Considerable improvements in medical interventions and healthcare management mean population aging has become a major public health concern worldwide. Cardiometabolic multimorbidity is defined as the co-existence of two or more of three cardiometabolic disorders: hypertension, diabetes mellitus, and cardiovascular disease (CVD). Cardiometabolic multimorbidity is becoming progressively more common globally, and the public health impact has received increased attention during the past several years.[1-3] The individual prevalence of each disease is increasing rapidly in China, along with significant changes in economic development and lifestyles.[4-7] Although some studies have evaluated the prevalence of multimorbidity in China using cross-sectional designs,[8-11] they have been limited by factors such as: small sample sizes, high risk of bias according to the Strengthening the Reporting of Observational Studies in Epidemiology guideline, restriction to older adult populations (>60 years), or including other chronic diseases (e.g., chronic obstructive pulmonary disease or cancer) in the definition of multimorbidity. Moreover, multimorbidity is a continuum, covering the transition from healthy status to development of a single disease and then progression to two or more diseases, with the possible addition of further diseases.[12] The term "evolution of multimorbidity" describes this process, which is generally evaluated from a longitudinal perspective. However, there have been limited studies on this topic, and none conducted among Chinese populations.

Multimorbidity is associated with high risk for mortality.[13-15] The Emerging Risk Factors Collaboration (ERFC) reported that mortality was similarly associated with a history of diabetes, stroke, or myocardial infarction (MI), and a multiplicative mortality risk was observed for any combination of these conditions in Western populations.[16] However, hypertension was not included in that evaluation, and time-varying exposure information to update multimorbidity status was not available. A study using a longitudinal design with continuous surveillance of cardiometabolic disease status in a general population in addition to using multimorbidity assessed at baseline may provide a better understanding of etiological associations and causality.

The CHinese Electronic Health Records Research in Yinzhou (CHERRY) study is a longitudinal cohort study involving 1,038,704 adults (22,750 deaths) from 2010 through 2016. Using CHERRY data, we aimed to provide reliable estimates about the prevalence of cardiometabolic comorbidities, investigate the evolution of multimorbidity during follow-up, and assess the association with mortality in a Chinese population.

METHODS

Study design

The CHERRY study is a longitudinal population-based ambispective cohort study focused on cardiovascular care and outcomes research. Individual participant data were extracted from the regional health information system in Yinzhou, an eastern coastal area of China. A detailed description of the data sources and cohort profile was published previously.[17] Specific data sources essential to the present study included: 1) the population census and registered health insurance database for individuals' general demographic characteristics; 2) health check databases, including health checks from the New Rural Cooperative Medical Scheme, older adults, and adults with hypertension and diabetes; 3) inpatient and outpatient electronic medical records (EMRs); 4) disease surveillance and management database that captured the incidence of CVD, hypertension, and diabetes (where cases were required to be reported for disease management by local general practitioners on confirmation of diagnosis); and 5) death certificates database where attribution of death refers to the primary cause provided by cause-specific mortality.

Individuals were included in the CHERRY study if they met all inclusion criteria: 1) aged ≥18 years on 1 January 2009; 2) had complete information on date of birth, sex, and a valid healthcare identifier; 3) had been living in Yinzhou for at least 6 months; and 4) had Chinese nationality. In total, 1,053,563 adults were originally enrolled in the CHERRY study. In this analysis, we choose 1 January 2010 as the date of inception to bypass the integration and preliminary test period of the EMR system and allow for better coverage of regional chronic

disease management services. After excluding those who died in 2009 or entered the system after 2016, we included 1,038,704 participants in this study (**Supplementary eFigure 1**). Follow-up in the health information system is generally continuous. CHERRY updates information for all cohort members annually from the health information system databases. Complete follow-up data were available for participants through to December 31, 2016. This study was approved by the Peking University Institutional Review Board (IRB00001052-16011).

Cardiometabolic multimorbidities and outcomes

Cardiometabolic multimorbidity was defined as the presence of two or more of three diagnosed disorders: hypertension, diabetes, or CVD [including coronary heart disease (CHD) and cerebrovascular diseases]. We categorized participants into eight groups: 1) hypertension, 2) diabetes, 3) CVD, 4) hypertension and diabetes, 5) hypertension and CVD, 6) diabetes and CVD, 7) hypertension, diabetes, and CVD, and 8) none of these diseases (reference group). Diagnosis of these cardiometabolic diseases (and date of diagnosis) were obtained from multiple sources: diseases management database (primary care), EMRs (hospital care), and disease surveillance database (disease registry). Date in disease surveillance was considered the gold standard for the date of diagnosis. Details of the comprehensive healthcare services for chronic disease surveillance and management provided in the study region were described previously.[17] In addition to individuals' baseline cardiometabolic disease status, longitudinal information for the exposure was also used. To evaluate the association between mortality and a history of hypertension, diabetes, CVD, and their cardiometabolic multimorbidities, changes in cardiometabolic disease status that occurred ≤30 days before death were excluded, assuming that there was a direct connection between the change of cardiometabolic multimorbidity status and mortality within the acute phase. The primary outcome was all-cause mortality during follow-up. Death was confirmed by the death certificate in the health information system, as previously described.[18] Diseases and deaths were classified according to the International Classification of Diseases, Tenth Revision (ICD-10).

Statistical analysis

Continuous and categorical baseline characteristics of participants were summarized by mean [standard deviation (SD)] or numbers (percentage) respectively. Cardiometabolic multimorbidities were classified as 8 combinations listed above. Numbers (and corresponding percentages) of participants who changed their cardiometabolic disease status during follow-up were summarized. Age- and sex- standardized prevalence and 95% confidence intervals (CI) for cardiometabolic multimorbidity at baseline and at the last visit were estimated for the overall population (and the population aged ≥40 years in a supplementary analysis) based on the distribution of the 2010 Chinese population census. A Poisson regression model adjusted for sex was used to calculate mortality rates, adjusted for age 60 years. To investigate the association between cardiometabolic multimorbidity and mortality, we first assessed the associations between the cardiometabolic multimorbidity groups at baseline and risk for death from any cause. Furthermore, cardiometabolic multimorbidity status was modeled as a time dependent exposure to enable updating of multimorbidity status during follow-up. Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazard regression models stratified by sex and adjusted for age in the primary analyses of the overall population, the population aged ≥40 years, and subgroups (sex, age, location [urban/rural], smoking status, and body mass index [BMI] category). To explore the extent to which conventional factors (BMI, smoking, education level, and location) explained the associations between cardiometabolic multimorbidity and mortality, HRs adjusted for these additional factors were calculated for people with full information on these factors. Finally, population attributable fractions (PAF) and 95% CI due to one, two or three cardiometabolic diseases were estimated by combining the proportional excess mortality (X_1, X_2, and X_3; where X=HR-1) and standard error in each category with the corresponding prevalence at baseline (P_1, P_2, and P_3).[19] The PAFs for one, two, or three disorders are P_1X_1/k, P_2X_2/k, and P_3X_3/k; where $k=1 + P_1X_1 + P_2X2 + P_3X_3$. PAFs were calculated based on: 1) the prevalence and HRs of cardiometabolic multimorbidity at baseline; and 2) the prevalence at last visit and HRs using time-variant cardiometabolic

multimorbidity status. All p-values were two-tailed and not adjusted for multiple testing. We used Stata (version 14.0) for all data analyses, with a statistical significance level of $P < 0.05$.

Patient and public involvement

Patients were not involved in the development of the research question or measures, or the design, recruitment, or conduct of this study. The results of this study will be disseminated to study participants and the public via this publication and the CHERRY study website (http://www.cherry-study.org).

RESULTS

The present cohort was established using the procedures listed in **Supplementary eFigure 1**. We began with 1.28 million permanent residents in Yinzhou, China with a valid personal identifier. After excluding subjects younger than 18 years old as at January 1, 2010, those that died before that date, and those entered into the system after December 31, 2016, the present analyses included 1,038,704 CHERRY study participants aged ≥18 years. **Table 1** shows participants' baseline characteristics. Among all participants, 1,025,542 (98.7%) had information on living location, 858,413 (82.6%) had information on education level, 905,987 (87.2%) had at least one BMI measurement, and 905,987 (88.7%) had at least one smoking status measurement. The mean±SD age at baseline was 42.5±14.8 years (51.4% women). The mean BMI was 22.5±2.5 kg/m^2. According to Asian-specific BMI cutoffs, 24.1% were overweight (23–25 kg/m^2) and 13.9% were obese (BMI ≥25 kg/m^2). At the last visit during follow-up, the mean BMI was 22.5±2.6 kg/m^2; 23.9% were overweight and 14.8% were obese. From baseline to the last visit, the proportion of former smokers changed from 2.2% to 2.4% and the proportion of current smokers changed from 18.9% to 20.0%.

Prevalence and evolution of cardiometabolic multimorbidity

At baseline, 85,684 participants had one diagnosed cardiometabolic disease, 22,871 had two diseases, and 2,203 had three diseases. The standardized prevalence were 9.32% (95%

CI: 9.26%–9.37%) for one disease, 2.57% (95% CI: 2.54%–2.60%) for two diseases, and 0.26% (95% CI: 0.25%–0.27%) for three diseases (**Table 2**). The estimated prevalence of diagnosed cardiometabolic multimorbidity increased with age and was higher in women than men (**Figure 1**). Among the population aged ≥40 years, the standardized prevalence rates were 16.82% (95% CI: 16.72%–16.92%) for one disease, 4.69% (95% CI: 4.65%–4.75%) for two diseases, and 0.47% (95% CI: 0.45%–0.49%) for three diseases (**Supplementary eTable 1**). In the population aged ≥60 years, the prevalence rates increased to 31.90% (95% CI: 31.65%–32.14%), 10.41% (95% CI: 10.25%–10.57%), and 1.20% (95% CI: 1.14%–1.26%) for one, two, and three diseases, respectively (**Supplementary eTable 2**).

In total, 105,209 participants (10.1%) changed their cardiometabolic multimorbidity status during the (median) 5-year follow-up (**Supplementary eTable 3**). Regarding the history of CVD, 50,458 (94.4%) of all 53,473 patients have information on type of CVD. Within these patients, 26,282 had CHD, 23,538 had cerebrovascular diseases and 638 had both CHD and cerebrovascular diseases respectively. The crude prevalence of cardiometabolic multimorbidity increased from 2.41% (95% CI: 2.38%–2.44%) to 5.94% (95% CI: 5.90%–5.99%) (**Figure 2 & Supplementary eTable 3**). Four disease groups (72,104 participants; 68.5%) lead all transitions during follow-up: 47,903 healthy subjects developed hypertension only; 8,388 healthy subjects developed diabetes only; 9,279 patients with hypertension developed CVD; and 6,534 patients with hypertension and diabetes developed CVD. Among 927,946 participants without any diagnosed cardiometabolic disease at baseline, 73,302 (7.9%) developed one or more cardiometabolic diseases, of which 47,903 (5.2%) developed hypertension only. Among 85,684 participants with one disease at baseline, 24,041 (28.1%) developed additional diseases. Of 69,406 participants with hypertension at baseline, 12,711 (18.31%) had an incidence of CVD during follow-up. Of 14,127 participants with diabetes at baseline, 5,386 (38.13%) had an incidence of CVD during follow-up. Finally, 7,865 (34.39%) of 22,871 participants with two diseases developed all three diseases during follow-up. The number of participants with all three

diseases increased from 2,203 at baseline to 18,547 by the end of the study (**Supplementary eTable 3**).

Associations with mortality

There were 22,750 deaths during the 5.43 million person-years of follow-up (median follow-up time, 5.16 years). The sex-adjusted all-cause mortality rate at age 60 years was 5.68 per 1000 person-years (6.50 in men, 4.91 in women). In the analysis using baseline cardiometabolic multimorbidity status, the age- and sex-adjusted HRs for mortality were 1.37 (95% CI: 1.33–1.42) for one disease, 1.71 (95% CI: 1.64–1.79) for two diseases, and 2.22 (95% CI: 2.00–2.46) for three diseases, compared with participants without any disease (**Figure 3**). The highest HRs were observed in patients with either a history of CVD only (3.31, 95% CI: 3.05–3.59) or diabetes and CVD (3.12, 95% CI: 2.37–4.11). Patients with hypertension only had lowest HR (1.26, 95% CI: 1.22–1.30). HRs for cardiometabolic multimorbidity were broadly similar in men and women, higher in younger participants (aged <40 years), and higher in those living in urban areas (**Supplementary eTable 4**). The sensitivity analysis for the analysis using baseline status excluding the initial 1 year of follow-up was broadly similar (**Supplementary eTable 5**).

The longitudinal data for cardiometabolic multimorbidity showed the age- and sex-adjusted HRs for mortality were broadly similar in those with one disease (1.36, 95% CI 1.32–1.41), higher in those with two diseases (2.03, 95% CI 1.96–2.10), and similar in those with all three diseases (2.16, 95% CI 2.05–2.29) compared with participants without any disease at the last visit (**Figure 3**). Although the pattern of HRs within each multimorbidity combination were broadly similar to the analysis using baseline status, the HR in participants with hypertension only reduced to 1.07 (95% CI 1.03–1.10), whereas that for those with history of CVD increased to 4.80 (95% CI 4.55–5.07). The HR in those with hypertension and diabetes was attenuated to 1.30 (95% CI 1.22–1.39), whereas that for participants with hypertension and CVD increased to 2.36 (95% CI 2.27–2.45). Broadly similar association were observed among the 788,703 participants with full information on additional risk

factors (BMI, smoking, education level and location) after further adjustment for those factors (**Supplementary eTable 6**).

PAFs

Using the prevalence and HRs for cardiometabolic disease status at baseline, the PAFs for all-cause mortality in the overall population aged ≥18 years due to one, two, and three cardiometabolic diseases were 3.30% (95% CI: 2.95%–3.65%), 1.73% (95% CI: 1.56%–1.90%), and 0.30% (95% CI: 0.25%–0.36%), respectively (**Table 3**). In people aged ≥40 years, the PAF increased to 5.10% (95% CI: 4.52%–5.68%) for one disease, 2.85% (95% CI: 2.56%–3.14%) for two diseases, and 0.50% (95% CI: 0.40%–0.59%) for three diseases. Using the prevalence at last visit and HRs for time-variant cardiometabolic disease status, PAFs were 4.17% (95% CI: 3.70%–4.63%) for one disease, 4.36% (95% CI: 4.07%–4.65%) for two diseases, and 2.13% (95% CI: 1.92%–2.35%) for three diseases. The overall PAF increased from 5.34% (95% CI: 4.96%–5.72%) to 10.66% (95% CI: 10.11%–11.21%).

DISCUSSION

Our analyses of more than 1 million Chinese adults (22,750 deaths during follow-up) in a longitudinal cohort provided estimates of the prevalence of cardiometabolic multimorbidity (hypertension, diabetes, and CVD) in a general population under real-world circumstances. This study also described the evolution of cardiometabolic diseases in this population over 5 years and evaluated associations with risk for all-cause mortality. Each of our main findings has potential implications.

First, 12.2% of Chinese adults aged ≥18 years in a real-world general population had at least one diagnosed cardiometabolic disease, and nearly 3% had cardiometabolic multimorbidity. Hypertension was the dominant diagnosis in the group with one disease. The prevalence of multimorbidity at baseline increased with age, and was 5.2% in the population aged ≥40 years and 11.6% in the population aged ≥60. One in four patients with any cardiometabolic disease had multimorbidity. This proportion was consistent in different

age groups. Moreover, the proportion of patients with multimorbidity more than doubled during the (median) 5-year follow-up. The proportion of patients with all three diseases increased to nine-fold the baseline prevalence (0.2% to 1.8%). Nearly 60% of patients with both hypertension and diabetes at baseline had an incidence of CVD during follow-up. Over 30% of patients with diabetes and 20% of patients with hypertension developed cardiometabolic multimorbidity. These findings highlighted the rapid progression of cardiometabolic diseases.

Limited publications are available on the epidemiology of multimorbidity in a general Chinese population. A systematic review of nine published studies in China reported the prevalence of multimorbidity among those aged ≥60 years ranged from 6.4% (95% CI: 5.1–8.0) to 76.5% (95% CI: 73.6–79.2).[10] However, most of the included studies considered morbidities in addition to cardiometabolic diseases and only reported prevalence based on number of diseases, which prevented us making direct comparisons. The estimated prevalence of single diagnosed diseases in our study was broadly consistent with estimates from national surveillance. For example, although the estimate of the prevalence of diabetes in China reached 10.9% in 2013, the national prevalence of diagnosed diabetes was only 4%.[4] Because our population was located in a developed area of China, our estimate of 3% is consistent with expectations, as the prevalence in this region is lower than the national estimate, even in traditional epidemiological surveys. Compared with developed countries, about 0.52% of participants aged ≥40 years (mean age 53.6±11.6 years) in our cohort had multimorbidity of diabetes and CVD (regardless of hypertension, 0.47%+0.05%=0.52%, **eTable 1**), which was similar as 0.7% reported in the UK Biobank (mean age 56.7±8.1 years).[16] About 1.3% of participants aged ≥60 years in our cohort had multimorbidity of diabetes and CVD, compared with 5% from a recent US survey involving people aged ≥65 years.[20] Previous studies in China and other countries have also shown that the prevalence of multimorbidity increased significantly with age.[9, 21] Older adults should therefore be a major population targeted for cardiometabolic multimorbidity prevention, considering population aging.

Second, over the 5-year follow-up we observed about a one-third higher mortality risk in patients with one condition at baseline, a two-thirds higher risk in patients with two diseases, and just over a two-fold higher risk in patients with all three diseases. Although these results may suggest that associations between mortality and hypertension, diabetes, and cardiovascular disease were additive in this population, we found significant heterogeneities within each disease combination. Patients with only hypertension at baseline had the lowest HR (1.26) and those with CVD only at baseline had a HR of 3.31. This pattern was aggravated by applying longitudinal cardiometabolic disease status information. The HR of patients with hypertension only reduced to 1.07 and that of patients with CVD only increased to 4.8. Among around 70,000 patients with hypertension at baseline, 15,000 developed additional cardiometabolic diseases, and therefore changed their disease status category. In addition, there were around 100,000 (10%) patients with hypertension in this study, and nearly half were identified during follow-up (i.e., suggesting that they were newly diagnosed). Therefore, the analysis using longitudinal disease status information showed that patients with hypertension had a lower HR than that using baseline status. In contrast, there was small number of patients (just over 2,000) with CVD only at baseline. Most patients with history of CVD also had diabetes or hypertension. Around 4,000 healthy participants at baseline developed CVD during follow-up. We speculated that the increment of the HR from 3.3 (baseline status) to 4.8 (longitudinal data) may be partly attributable to the relative short-term high risk after a first-ever CVD event. Similarly, we found an increased risk for those with both hypertension and CVD in the longitudinal analysis compared with that using baseline status.

Regardless of the existence of other diseases, a history of CVD tended to dominate risk for mortality, especially over the 5 years of follow-up. Among patients with any cardiometabolic disease, patients with CVD only had the highest risk, which may reflect a short-term effect of newly diagnosed CVD. Alternatively, it may also indicate that patients with other cardiometabolic diseases (e.g., hypertension or diabetes) were likely to be more aware of

their health condition. Moreover, among those with cardiometabolic multimorbidity, only patients with hypertension and diabetes had significantly lower HR, whereas other groups (i.e., all with CVD) were broadly similar, even those with all three diseases.

Regarding the HRs for mortality from our study, we compared our findings with other studies. In ERFC study (involving 91 cohort studies, mainly Western populations)[16], the estimated HR for mortality was about 2 in participants with one cardiometabolic multimorbidity condition (type 2 diabetes, coronary heart disease, and stroke) and the association was multiplicative. However, they did not include hypertension and only used baseline disease status. We observed a broadly similar HR for patients with diabetes. The higher HR for patients with CVD (stroke or MI) in our population might be explained by differences in the overall healthcare services across countries with different economic levels. The estimated HR for patients with CVD and diabetes (regardless of hypertension) in our study was around 2.5, which was lower than the ERFC estimate (around 3.5–4), but consistent with the Hispanic Established Population for the Epidemiological study of the Elderly (at 2.4).[22] This may imply that ethnic disparity could explain the differences. We also showed that cardiometabolic multimorbidity had a more serious impact on those living in urban areas compared with rural areas. This suggests it is important to consider location differences in developing strategies to improve public health.

The strength of this study was that it was a large-scale, comprehensive study under real-world circumstances. We used longitudinal data for cardiometabolic disease status to assess the prevalence and evolution of cardiometabolic multimorbidity during follow-up. However, this study also had several limitations. First, the CHERRY study is based on a regional population in a developed area of China, and is not nationally representative. Second, this study had relatively short follow-up period and the long-term effect of cardiometabolic multimorbidity needs to be further evaluated. Third, the accurate time of disease onset, especially hypertension and diabetes, were not available. We could only approximate this information using the first diagnosis time for these diseases. Information on medication use

and risk control was also not available. Finally, our laboratory data sources included lipids measurements for only 25%–30% of the population, which prevented us from model adjustment for conventional lipids risk factors. However, the ERFC results showed broadly similar HRs for cardiometabolic multimorbidity and mortality after further adjustment for smoking, BMI, systolic blood pressure, high-density lipoprotein, total cholesterol, socioeconomic status, and diet.[16]

Conclusions

The prevalence of patients with cardiometabolic multimorbidity in a general population in China more than doubled over 5 years, indicating a rapid evolution of cardiometabolic multimorbidity. Among all combinations, history of CVD leads the risk for mortality. Our findings highlight the need for a complementary strategy for primary and secondary prevention of cardiometabolic diseases in China.

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Data sharing statement

No additional data available.

Authors' contributions

DZ, XT, and PG drafted the manuscript. DZ, XT, PS, and PG conceived and designed the study. DZ, YS, and HL made substantial contributions to the study design. XT, XL, PS and HL are responsible for study coordination; XT, PS, JW, JZ and HL are responsible for data quality control; DZ, PL, and YS are responsible for data wrangling; XT, DZ, YS, XL, ZX and PG are responsible for data analysis. All authors contributed to the writing of the manuscript in an iterative manner, and have read and approved the final manuscript.

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Competing interests

None declared.

References

1. Tinetti ME, Fried TR, Boyd CM. Designing health care for the most common chronic condition--multimorbidity. Jama 2012;307(23):2493-4. doi: 10.1001/jama.2012.5265 [published Online First: 2012/07/17]

2. Glynn LG. Multimorbidity: another key issue for cardiovascular medicine. Lancet 2009;374(9699):1421-2. doi: 10.1016/s0140-6736(09)61863-8 [published Online First: 2009/10/27]

3. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380(9836):37-43. doi: 10.1016/S0140-6736(12)60240-2

4. Wang L, Gao P, Zhang M, et al. Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. Jama 2017;317(24):2515-23. doi: 10.1001/jama.2017.7596

5. Wang W, Jiang B, Sun H, et al. Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults. Circulation 2017;135(8):759-71. doi: 10.1161/circulationaha.116.025250 [published Online First: 2017/01/06]

6. Chen WW, Gao RL, Liu LS, et al. China cardiovascular diseases report 2015: a summary. Journal of geriatric cardiology : JGC 2017;14(1):1-10. doi: 10.11909/j.issn.1671-5411.2017.01.012 [published Online First: 2017/03/09]

7. Wu Y, Benjamin EJ, MacMahon S. Prevention and Control of Cardiovascular Disease in the Rapidly Changing Economy of China. Circulation 2016;133(24):2545-60. doi: 10.1161/circulationaha.115.008728 [published Online First: 2016/06/15]

8. Wang SB, D'Arcy C, Yu YQ, et al. Prevalence and patterns of multimorbidity in northeastern China: a cross-sectional study. Public Health 2015;129(11):1539-46. doi: 10.1016/j.puhe.2015.06.013

9. Wang HH, Wang JJ, Wong SY, et al. Epidemiology of multimorbidity in China and implications for the healthcare system: cross-sectional survey among 162,464 community

household residents in southern China. BMC Med 2014;12:188. doi: 10.1186/s12916-014-0188-0 [published Online First: 2014/10/24]

10. Hu X, Huang J, Lv Y, et al. Status of prevalence study on multimorbidity of chronic disease in China: systematic review. Geriatr Gerontol Int 2015;15(1):1-10. doi: 10.1111/ggi.12340

11. Gu J, Chao J, Chen W, et al. Multimorbidity in the community-dwelling elderly in urban China. Arch Gerontol Geriatr 2017;68:62-67. doi: 10.1016/j.archger.2016.09.001 [published Online First: 2016/09/23]

12. Ruel G, Levesque JF, Stocks N, et al. Understanding the evolution of multimorbidity: evidences from the North West Adelaide Health Longitudinal Study (NWAHS). PloS one 2014;9(5):e96291. doi: 10.1371/journal.pone.0096291 [published Online First: 2014/05/07]

13. Bragg F, Holmes MV, Iona A, et al. Association Between Diabetes and Cause-Specific Mortality in Rural and Urban Areas of China. Jama 2017;317(3):280-89. doi: 10.1001/jama.2016.19720

14. Yang G, Wang Y, Zeng Y, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet 2013;381(9882):1987-2015. doi: 10.1016/s0140-6736(13)61097-1 [published Online First: 2013/06/12]

15. Lewington S, Lacey B, Clarke R, et al. The Burden of Hypertension and Associated Risk for Cardiovascular Mortality in China. JAMA internal medicine 2016;176(4):524-32. doi: 10.1001/jamainternmed.2016.0190 [published Online First: 2016/03/15]

16. Emerging Risk Factors C, Di Angelantonio E, Kaptoge S, et al. Association of Cardiometabolic Multimorbidity With Mortality. JAMA 2015;314(1):52-60. doi: 10.1001/jama.2015.7008

17. Lin H, Tang X, Shen P, et al. Using big data to improve cardiovascular care and outcomes in China: a protocol for the CHinese Electronic health Records Research in Yinzhou (CHERRY) Study. BMJ Open 2018;8(2):e019698. doi: 10.1136/bmjopen-2017-019698 [published Online First: 2018/02/15]

18. Wang JB, Gu MJ, Shen P, et al. Body Mass Index and Mortality: A 10-Year Prospective

Study in China. Scientific reports 2016;6:31609. doi: 10.1038/srep31609 [published Online First: 2016/08/23]

19. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388(10046):776-86. doi: 10.1016/s0140-6736(16)30175-1 [published Online First: 2016/07/18]

20. Weiss CO, Boyd CM, Yu Q, et al. Patterns of prevalent major chronic disease among older adults in the United States. Jama 2007;298(10):1160-2 doi: 10.1001/jama.298.10.1160-b[published Online First: Epub Date]

21. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012;380(9836):37-43 doi: 10.1016/s0140-6736(12)60240-2[published Online First: Epub Date]

22. Otiniano ME, Du XL, Ottenbacher K, et al. The effect of diabetes combined with stroke on disability, self-rated health, and mortality in older Mexican Americans: results from the Hispanic EPESE. Arch Phys Med Rehabil 2003;84(5):725-30. [published Online First: 2003/05/09]

Table 1. Characteristics of participants at baseline.

	Participants ≥18 years	Participants ≥40 years
No. (%) of participants	1,038,704	545,632
Age (at baseline) mean (SD)	42.51 (14.84)	53.58 (11.63)
Body mass index (kg/m²) mean (SD)	22.48 (2.53)	22.94 (2.66)
BMI (kg/m² Asian-specific cutoffs)		
<23 (Normal)	562,106 (62.04)	264,283 (53.65)
23-<25 (Overweight)	218,019 (24.06)	134,411 (27.29)
≥25 (Obese)	125,862 (13.89)	93,869 (19.06)
Gender No. (%)		
Male	504,525 (48.57)	275,382 (50.47)
Female	534,179 (51.43)	270,250 (49.53)
Location No. (%)		
Urban	316,900 (30.90)	168,208 (31.18)
Rural	708,642 (69.10)	371,311 (68.82)
Education levels No. (%)		
Primary school or lower	249,881 (29.11)	219,934 (45.78)
Middle school	547,890 (63.83)	248,425 (51.71)
College or higher	60,642 (7.06)	12,046 (2.51)
Smoking status (Current) No. (%)		
Never	726,241 (78.87)	388,223 (77.15)
Former smoker	20,524 (2.23)	17,678 (3.51)
Current smoker	174,084 (18.90)	97,328 (19.34)

Table 2. Standardized prevalence of cardiometabolic disease status at baseline.

	Overall (N=1,038,704)		Male (N=504,525)		Female (N=534,179)	
	No. of cases	**% (95% CI)**	**No. of cases**	**% (95% CI)**	**No. of cases**	**% (95% CI)**
One disease	85,684	9.32 (9.26-9.37)	40,883	8.64 (8.57-8.72)	44,801	10.01 (9.93-10.09)
HT	69,406	7.60 (7.55-7.65)	32,697	6.96 (6.89-7.02)	36,709	8.25 (8.18-8.33)
DM	14,127	1.49 (1.46-1.51)	6,992	1.43 (1.40-1.47)	7,135	1.54 (1.51-1.58)
CVD	2,151	0.23 (0.22-0.24)	1,194	0.25 (0.24-0.27)	957	0.21 (0.20-0.23)
Two diseases	22,871	2.57 (2.54-2.60)	10,349	2.24 (2.20-2.29)	12,522	2.90 (2.85-2.95)
HT+DM	11,073	1.26 (1.24-1.29)	4,722	1.03 (1.00-1.06)	6,351	1.50 (1.46-1.53)
HT+CVD	11,540	1.28 (1.25-1.30)	5,481	1.18 (1.15-1.21)	6,059	1.38 (1.34-1.41)
DM+CVD	258	0.03 (0.02-0.03)	146	0.03 (0.03-0.04)	112	0.03 (0.02-0.03)
Three diseases	2,203	0.26 (0.25-0.27)	841	0.19 (0.17-0.20)	1,362	0.33 (0.31-0.35)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Table 3. Population attributable fractions for cardiometabolic multimorbidity.

	Multimorbidity (% [95% CI])			
	1 disease	**2 diseases**	**≥3 diseases**	**Total**
Using the prevalence and HRs of cardiometabolic multimorbidity at baseline				
Participants ≥ 18years	3.30 (2.95-3.65)	1.73 (1.56-1.90)	0.30 (0.25-0.36)	5.34 (4.96-5.72)
Men	3.10 (2.65-3.54)	1.45 (1.24-1.65)	0.18 (0.12-0.24)	4.72 (4.24-5.21)
Women	3.68 (3.13-4.22)	2.11 (1.83-2.39)	0.44 (0.35-0.54)	6.23 (5.62-6.83)
Participants ≥ 40years	5.10 (4.52-5.68)	2.85 (2.56-3.14)	0.50 (0.40-0.59)	8.44 (7.82-9.07)
Participants ≥ 60years	6.11 (5.07-7.16)	4.60 (4.01-5.18)	0.96 (0.75-1.17)	11.67 (10.54-12.81)
Using the prevalence at last visit and HRs using time-variant cardiometabolic multimorbidity status				
Participants ≥ 18years	4.17 (3.70-4.63)	4.36 (4.07-4.65)	2.13 (1.92-2.35)	10.66 (10.11-11.21)
Men	4.19 (3.57-4.82)	4.14 (3.76-4.52)	1.69 (1.43-1.94)	10.02 (9.30-10.75)
Women	4.33 (3.62-5.05)	4.75 (4.30-5.20)	2.71 (2.35-3.07)	11.80 (10.95-12.64)
Participants ≥ 40years	5.92 (5.18-6.65)	6.95 (6.48-7.41)	3.49 (3.13-3.84)	16.35 (15.52-17.18)
Participants ≥ 60years	6.47 (5.36-7.58)	11.03 (10.19-11.88)	5.75 (5.09-6.41)	23.25 (21.98-24.53)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Figure legends

Figure 1. Prevalence of cardiometabolic disease according to age groups.

Note: HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Figure 2. Evolution of cardiometabolic disease status during follow-up.

Note: *Crude prevalence; HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Figure 3. Age- and sex-adjusted HRs (95%) for all-cause mortality by cardiometabolic disease status.

Note: HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

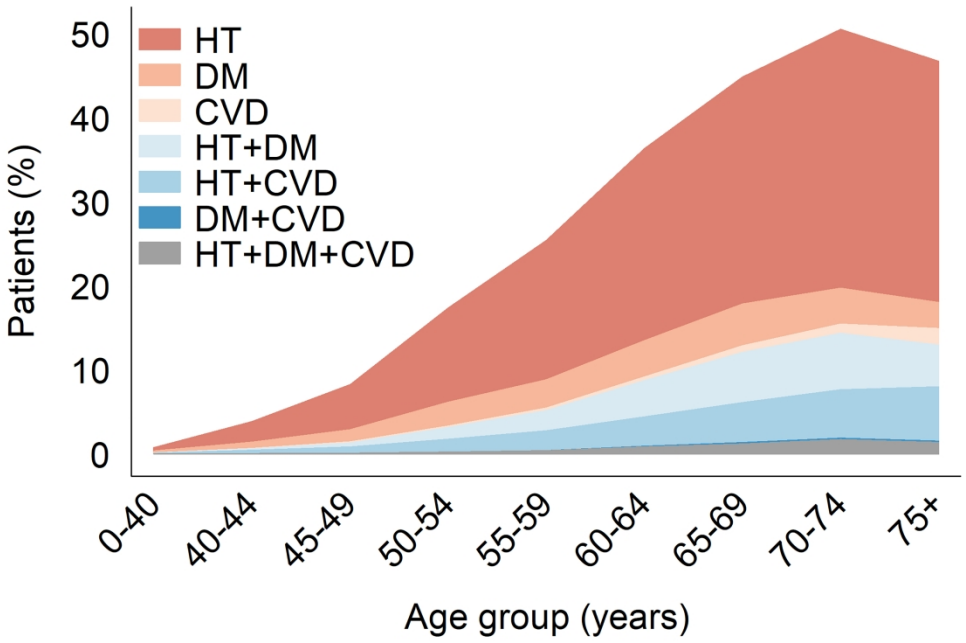


Figure 1. Prevalence of cardiometabolic disease according to age groups.

299x199mm (300 x 300 DPI)

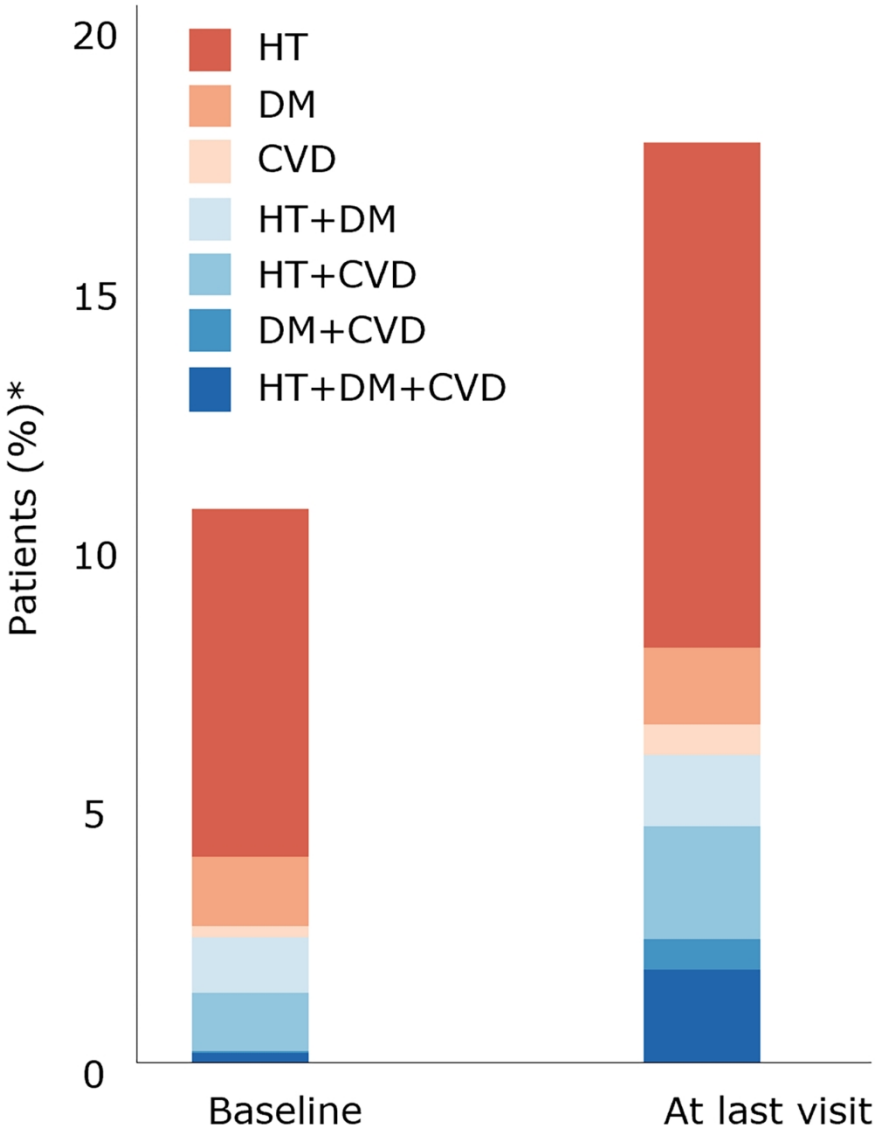


Figure 2. Evolution of cardiometabolic disease status during follow-up.

153x199mm (300 x 300 DPI)

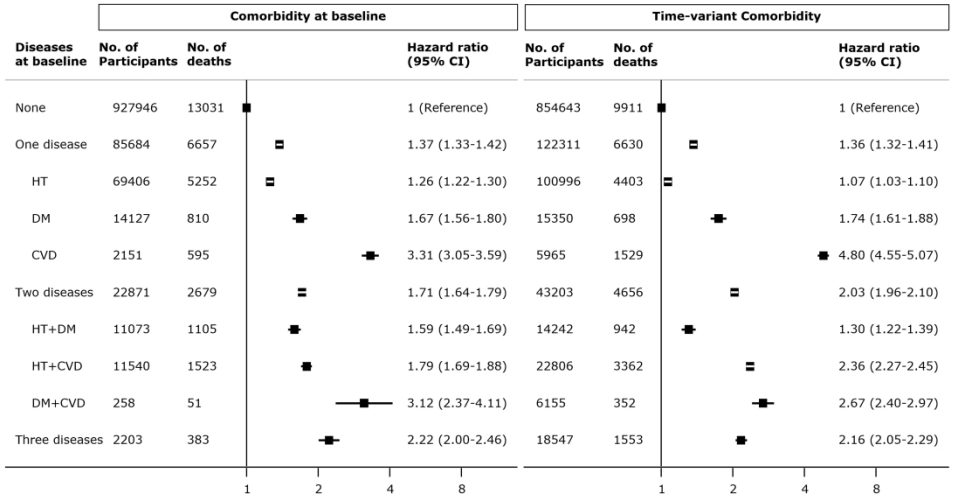


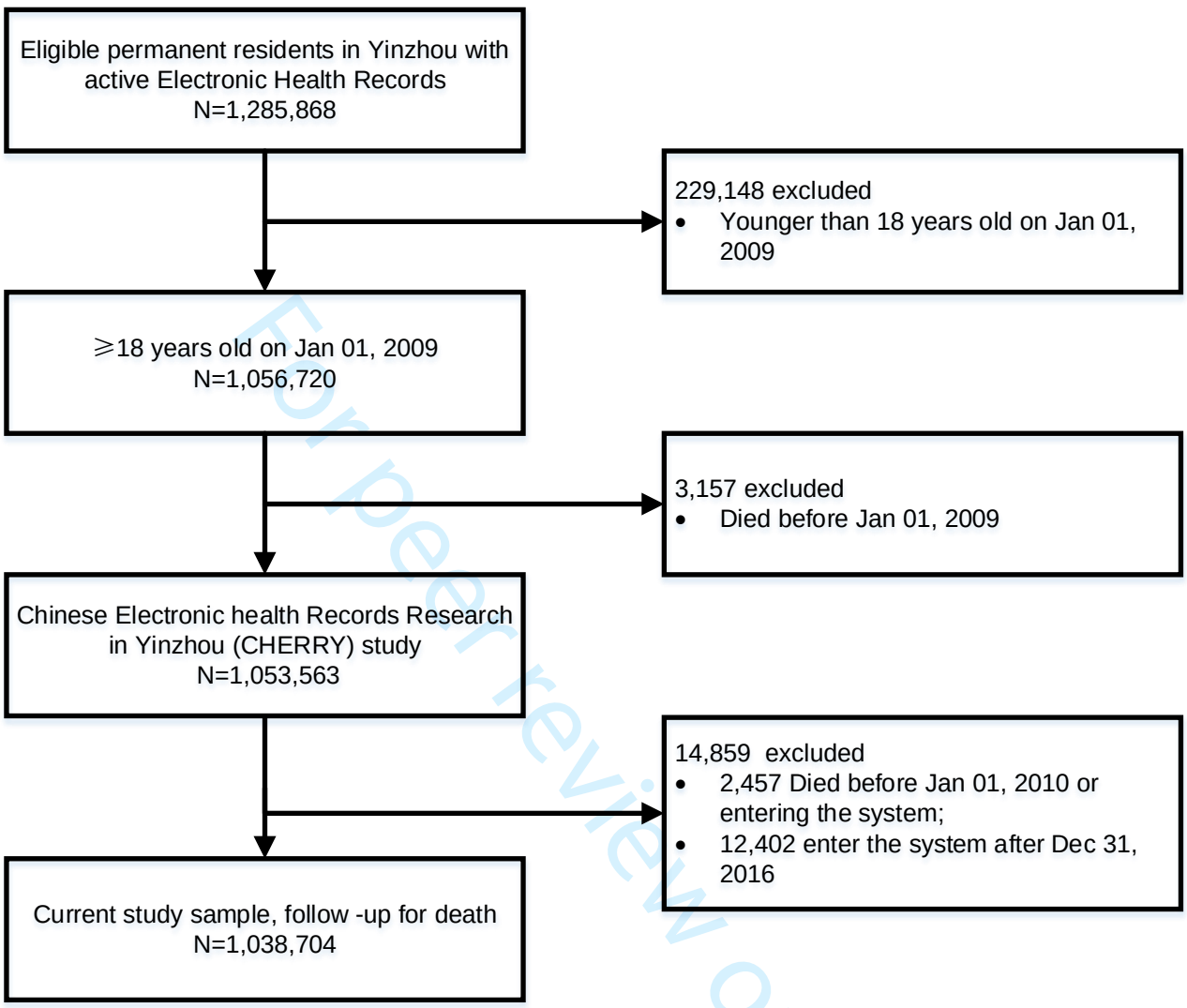
Figure 3. Age- and sex-adjusted HRs (95%) for all-cause mortality by cardiometabolic disease status.

371x199mm (300 x 300 DPI)

Supplementary Material

Multimorbidity of cardiometabolic diseases: Prevalence and Risk of Mortality from One Million Chinese Adults in a Longitudinal Cohort Study

eFigure 1. Flow chart of inclusion of participants in CHERRY study.



eTable 1. Standardized prevalence of cardiometabolic multimorbidity at baseline (age≥40 years).

	Overall (N=545,632)		Male (N=275,382)		Female (N=270,250)	
	No. of cases	% (95% CI)	No. of cases	% (95% CI)	No. of cases	% (95% CI)
One disease	82,589	16.82 (16.72-16.92)	39,133	15.54 (15.40-15.68)	43,456	18.11 (17.96-18.26)
HT	67,505	13.81 (13.71-13.90)	31,512	12.58 (12.46-12.71)	35,993	15.05 (14.91-15.19)
DM	13,041	2.59 (2.55-2.64)	6,481	2.50 (2.44-2.57)	6,560	2.68 (2.62-2.75)
CVD	2,043	0.42 (0.40-0.44)	1,140	0.45 (0.43-0.48)	903	0.38 (0.35-0.40)
Two diseases	22,405	4.69 (4.65-4.75)	10,065	4.09 (4.01-4.16)	12,340	5.31 (5.22-5.40)
HT+DM	10,966	2.33 (2.28-2.36)	4,656	1.90 (1.85-1.96)	6,310	2.76 (2.69-2.82)
HT+CVD	11,186	2.31 (2.27-2.36)	5,268	2.12 (2.07-2.18)	5,918	2.50 (2.44-2.57)
DM+CVD	253	0.05 (0.05-0.06)	141	0.06 (0.05-0.07)	112	0.05 (0.04-0.06)
Three diseases	2,185	0.47 (0.45-0.49)	828	0.34 (0.32-0.37)	1,357	0.60 (0.57-0.64)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

eTable 2. Standardized prevalence of cardiometabolic multimorbidity at baseline (age≥60 years).

	Overall (N=61,339)		Male (N=28,431)		Female (N=32,908)	
	No. of cases	% (95% CI)	No. of cases	% (95% CI)	No. of cases	% (95% CI)
One disease	45,083	31.90 (31.65-32.14)	21,351	30.06 (29.72-30.40)	23,732	33.66 (33.31-34.01)
HT	37,777	26.77 (26.54-27.00)	17,807	25.12 (24.80-25.44)	19,970	28.36 (28.02-28.70)
DM	5,833	4.12 (4.02-4.23)	2,733	3.84 (3.70-3.98)	3,100	4.39 (4.24-4.54)
CVD	1,473	1.00 (0.95-1.06)	811	1.10 (1.03-1.18)	662	0.91 (0.84-0.98)
Two diseases	14,597	10.41 (10.25-10.57)	6,448	9.11 (8.90-9.33)	8,149	11.65 (11.41-11.90)
HT+DM	7,398	5.32 (5.20-5.44)	3,057	4.33 (4.18-4.49)	4,341	6.26 (6.08-6.45)
HT+CVD	7,005	4.96 (4.84-5.07)	3,288	4.64 (4.48-4.79)	3,717	5.27 (5.10-5.44)
DM+CVD	194	0.13 (0.11-0.15)	103	0.14 (0.11-0.17)	91	0.12 (0.10-0.15)
Three diseases	1,659	1.20 (1.14-1.26)	632	0.89 (0.82-0.96)	1,027	1.49 (1.40-1.58)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

eTable 3. Evolution of cardiometabolic disease status during follow-up.

Number of disorders at baseline	Number of disorders at last visit										
	None	**One disease**	HT	DM	CVD	**Two diseases**	HT+DM	HT+CVD	DM+CVD	**Three diseases**	**Total**
None	854,643 (92.1%)	60,668 (6.5%)	47,903 (5.2%)	8,388 (0.9%)	4,377 (0.5%)	9,931 (1.1%)	4,322 (0.5%)	2,798 (0.3%)	2,811 (0.30%)	2,704 (0.3%)	927,946 (89.3%)
One disease		61,643 (71.9%)				18,266 (21.3%)				5,775 (6.7%)	85,684 (8.2%)
HT			53,093 (76.5%)				3,602 (5.2%)	9,279 (13.4%)		3,432 (4.9%)	69,406 (6.7%)
DM				6,962 (49.3%)			1,779 (12.6%)		3,121 (22.1%)	2,265 (16.0%)	14,127 (1.4%)
CVD					1,588 (73.8%)			437 (20.3%)	48 (2.2%)	78 (3.6%)	2,151 (0.2%)
Two diseases						15,006 (65.6%)				7,865 (34.4%)	22,871 (2.2%)
HT+DM							4,539 (41.0%)			6,534 (59.0%)	11,073 (1.1%)
HT+CVD								10,292 (89.2%)		1,248 (10.8%)	11,540 (1.1%)
DM+CVD									175 (67.8%)	83 (32.2%)	258 (0.0%)
Three diseases										2,203	2,203 (0.2%)
Total	854,643 (82.28%)	122,311 (11.78%)	100,996 (9.72%)	15,350 (1.48%)	5,965 (0.57%)	43,203 (4.16%)	14,242 (1.37%)	22,806 (2.20%)	6,155 (0.59%)	18,547 (1.79%)	1,038,704

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

eTable 4. Age- and sex-adjusted HRs (95%) for all-cause mortality by cardiometabolic multimorbidity at baseline according to individuals' subgroups.

Subgroup		Number of disorders	n (total)	n (death)	HR (95% CI)
Gender	**Men**	0	452,452	7,390	1
		1	40,883	3,481	1.38 (1.32-1.43)
		2	10,349	1,316	1.68 (1.58-1.78)
		3	841	155	2.01 (1.71-2.36)
	Women	0	475,494	5,641	1
		1	44,801	3,176	1.39 (1.33-1.45)
		2	12,522	1,363	1.78 (1.67-1.88)
		3	1,362	228	2.44 (2.14-2.78)
Age groups	**<40 years**	0	489,493	391	1
		1	3,095	22	4.74 (3.06-7.33)
		≥2	484	2	1.91 (0.47-7.67)
	40-59 years	0	356,879	2,856	1
		1	37,506	538	1.10 (1.00-1.21)
		2	7,808	157	1.32 (1.13-1.56)
		3	526	16	1.87 (1.14-3.05)
	≥60 years	0	81,574	9,784	1
		1	45,083	6,097	1.22 (1.18-1.26)
		2	14,597	2,520	1.50 (1.44-1.57)
		3	1,659	367	1.91 (1.72-2.12)
BMI (kg/m2 Asian-specific cutoffs)	**<23 (Normal)**	0	520,434	6,971	1
		1	33,112	3,407	1.18 (1.13-1.23)
		2	7,879	1,223	1.47 (1.38-1.56)
		3	681	141	1.79 (1.51-2.11)
	23-<25 (Overweight)	0	187,405	2,617	1
		1	23,757	1,490	0.98 (0.92-1.04)
		2	6,294	588	1.16 (1.06-1.27)
		3	563	94	1.61 (1.31-1.98)
	≥25 (Obese)	0	89,870	1,430	1

		1	26,650	1,266	0.98 (0.90-1.05)
		2	8,404	705	1.32 (1.21-1.45)
		3	938	132	1.85 (1.55-2.21)
BMI (kg/m2)	**<25 (Normal)**	0	707,839	9,588	1
		1	56,869	4,897	1.10 (1.07-1.14)
		2	14,173	1,811	1.34 (1.28-1.41)
		3	1,244	235	1.71 (1.50-1.94)
	25-<30 (Overweight)	0	84,326	1,325	1
		1	23,991	1,132	0.97 (0.90-1.05)
		2	7,459	612	1.30 (1.18-1.43)
		3	804	115	1.86 (1.53-2.25)
	≥30 (Obese)	0	5,544	105	1
		1	2,659	134	1.01 (0.78-1.31)
		2	945	93	1.55 (1.17-2.06)
		3	134	17	1.79 (1.07-3.00)
Smoking status	**Current smoker**	0	162,325	1,762	1
		1	9,186	615	1.27 (1.15-1.39)
		2	2,411	236	1.50 (1.31-1.72)
		3	162	30	2.81 (1.96-4.04)
	Non-current smoker	0	650,393	10,132	1
		1	73,932	5,914	1.16 (1.12-1.20)
		2	20,400	2,433	1.45 (1.39-1.52)
		3	2,040	352	1.83 (1.64-2.03)
Region	**Rural**	0	638,725	10,421	1
		1	53,347	5,343	1.39 (1.35-1.44)
		2	15,043	2,015	1.57 (1.50-1.65)
		3	1,527	295	2.01 (1.79-2.25)
	Urban	0	279,407	2,521	1
		1	29,368	1,267	1.30 (1.21-1.39)
		2	7,468	628	2.06 (1.89-2.25)
		3	657	84	2.54 (2.04-3.15)

eTable 5. Age- and sex-adjusted HRs (95%) for all-cause mortality by cardiometabolic multimorbidity at baseline exclude follow-up less than one year.

Diseases at baseline	No. of Participants	No. of deaths	HR (95% CI)
None	916,681	10,941	1
One diseases	82,959	5,945	1.46 (1.42-1.51)
HT	67,560	4,767	1.35 (1.31-1.40)
DM	13,443	729	1.83 (1.70-1.97)
CVD	1,956	449	3.10 (2.82-3.40)
Two diseases	22,393	2,394	1.82 (1.74-1.90)
HT+DM	10,848	1,024	1.75 (1.64-1.87)
HT+CVD	11,317	1,331	1.85 (1.74-1.95)
DM+CVD	228	39	3.07 (2.24-4.20)
Three diseases	2,142	343	2.36 (2.12-2.63)

HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease

eTable 6. HRs (95%) for all-cause mortality in participants with full information on cardiovascular risk factors and other characteristics (≥18 years, baseline vs repeat exclude diseases in 30 days of death).

	No. of Participants	No. of Deaths	Model 1 Age and Sex	Model 2 Age, Sex and BMI	Model 3 Age, Sex and Smoking	Model 4 Age, Sex, Smoking and BMI	Model 5 Age, Sex, Smoking, BMI, Education and Region
Comorbidity at baseline							
0	687,478	10,607	1	1	1	1	1
1	77,125	6,019	1.04 (1.01, 1.07)	1.03 (0.99, 1.06)	1.08 (1.04, 1.11)	1.06 (1.03, 1.10)	1.09 (1.06, 1.13)
2	21,945	2,470	1.26 (1.21, 1.32)	1.25 (1.19, 1.31)	1.33 (1.28, 1.40)	1.32 (1.26, 1.38)	1.35 (1.29, 1.41)
3	2,155	363	1.64 (1.48, 1.82)	1.63 (1.47, 1.81)	1.77 (1.60, 1.97)	1.76 (1.58, 1.95)	1.79 (1.61, 1.98)
Comorbidity during follow-up							
0	617,490	7,743	1	1	1	1	1
1	111,227	5,872	0.96 (0.93, 1.00)	0.95 (0.92, 0.98)	1.00 (0.97, 1.04)	0.98 (0.95, 1.02)	1.02 (0.98, 1.06)
2	41,634	4,330	1.38 (1.32, 1.43)	1.37 (1.31, 1.42)	1.46 (1.40, 1.51)	1.45 (1.39, 1.50)	1.46 (1.40, 1.51)
3	18,352	1,514	1.43 (1.35, 1.51)	1.41 (1.33, 1.49)	1.56 (1.47, 1.65)	1.53 (1.45, 1.62)	1.57 (1.48, 1.66)

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 2 2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1, 2 2 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6		
Objectives	3	State specific objectives, including any prespecified hypotheses	6		
Methods					
Study Design	4	Present key elements of study design early in the paper	6-7		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	6-7 Not applied	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6, 7, eFigure 1 6, 7, eFigure 1 6-7, protocol (BMJ open 2018; 8(2): e019698)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7-8	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7-8
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7, protocol (BMJ open 2018; 8(2): e019698)		

Bias	9	Describe any efforts to address potential sources of bias	6-7		
Study size	10	Explain how the study size was arrived at	6-7, eFigure 1		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7-8		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	8 8 15 7 8		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	6-7, eFigure 1

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	6-7, eFigure 1
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	6-7, protocol (BMJ open 2018; 8(2): e019698)
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	6-7, 9, eFigure 1 7, eFigure 1 eFigure 1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	6-7, eFigure 1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Table 1 9		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	11, Figure 3		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Figure 3, eTable 4, 5, 6 9 12		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	eTable 4, 5, 6		
Discussion					
Key results	18	Summarise key results with reference to study objectives	9-12		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	4, 14-16		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	4, 16		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	4, 6

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.