PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multimorbidity of Cardiometabolic Diseases: Prevalence and Risk for Mortality from 1 Million Chinese Adults in a Longitudinal Cohort Study
AUTHORS	Zhang, Dudan; TANG, Xun; Shen, Peng; Si, Yaqin; Liu, Xiaofei; Xu, Zhe; Wu, Jinguo; Zhang, Jingyi; Lu, Ping; Lin, Hongbo; GAO, Pei

VERSION 1 – REVIEW

REVIEWER	Yang, Ling University of Oxford Nuffield Department of Population Health
REVIEW RETURNED	19-Jun-2018

GENERAL COMMENTS	This paper aimed to estimate the prevalence of cardiometablick comorbiditties and investigate the progress of multimorbidity in a study from a developed region in east China through the linkage with all available health information systems for the local residents. The data quality for those health information systems may need to be more explained and clarified. Although large sample size with rich information included and detailed data presented, given only one developed area covered, the prevalence and trends of cardiometabolic multimorbidity presented from this study may not applicable to other places and certainly not be representable for Chinese population. This significantly reduced the scientific value of the paper and it would be more valuable if including analyses on the associations between various risk factors and the cardiometabolic multimorbidities.

REVIEWER	Evangelos Liberopoulos University of Ioannina, Greece
REVIEW RETURNED	27-Jul-2018

GENERAL COMMENTS	Zhang et al analyzed big data from 1,038,704 Chinese individuals from the CHERRY database. There were 22,750 deaths after a follow-up of 5.16 years. They showed that during follow-up the prevalence of multimorbidity (hypertension, diabetes and CVD) more than doubled, with CVD contributing mostly to the risk of death. The study is of interest, the manuscript is well written, the analysis is sound and the conclusions are justified by the results. Comments: 1. The results are somehow anticipated. It is known from previous studies that the prevalence of CVD and CVD risk factors is increasing in the Chinese population and that history of CVD is associated with increased risk of CVD and total death. 2. A lot of information is missing: type of CVD, risk factor control, medications, change of BMI, change of smoking status, etc.

REVIEWER	Clement Kufe, NYUYKI
	University of the Witwatersrand, Johannesburg, South Africa
REVIEW RETURNED	03-Aug-2018

GENERAL COMMENTS	Cardiometabolic comorbidity data are critical developing appropriate interventions.
	The study described prevalence and hazard ratios of a population in an urban area using data from medical records. It gives insights on the evolution of cardiometabolic conditions.
	Page 2: Abstract: Results: Lines 37-40 and 46 – 50 describe the same results?
	Page 3: Abstract: Last sentence: A complementary strategy of what is needed in the Chinese population?
	Strengths and limitations: Remove "under real world circumstances"
	Page 5, Line 34: The term of "evolution of multimorbidity" …Remove of after the word term.
	Page 7: Line 78: "Participants is generally……" re-phrase Statistical Analysis
	Indicate rather how descriptive and inferential anlaysis was done.
	Page 8: Line 110-113: Remove is part of results.
	Page 8: Line 111: Re-phrase Numbers the corresponding percentages of participants who changed their cardiometabolic disease status within each 8 combination listed above were summarized.
	Page 8: Line 129: Re-phrase "We judged p values less than 0.05 significant".
	Page 9: Lines 148 – 150. Re-phrase "The estimated prevalence for the diagnosed cardiometabolic comorbidity was generally increased along with age and higher in women". It could as well be re-written "The estimated prevalence for the diagnosed cardiometabolic comorbidity increased with age and was higher in women than men".
	Page 9 and 10: Re-write the sentence, Line 160-163
	Page 10: Re-write the sentence, Lines 165-166. Not advisable to start a sentence with a number.
	Page 11: Line 217 rather than investigated write described…… Discussion
	Page 12: Line 224-226. How do these results compare with other studies?
	Page 13: Lines 249 – 260. How do these results compare with other studies?
	Page 14: Line 290-293: Is the conclusion from this study which is in an urban setting or from another study. A reference is needed to compare with studies in rural settings.
	eTable 3: Correct lase in the sentence: "Number of disorders at lase visit"
	General Comments
	English needs to be reviewed.
	The discussion should be underpinned with comparison to results of studies elsewhere. The authors need to these comparisons.
	Was the data complete for all the participants? If not, indicate the number and percentages of missing data points for each of the covariates and the methods used to address this. Was any multiple imputation done to complete the data?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Overview: This paper aimed to estimate the prevalence of cardiometabolic comorbidities and investigate the progress of multimorbidity in a study from a developed region in east China through the linkage with all available health information systems for the local residents. The data quality for those health information systems may need to be more explained and clarified. Although large sample size with rich information included and detailed data presented, given only one developed area covered, the prevalence and trends of cardiometabolic multimorbidity presented from this study may not applicable to other places and certainly not be representable for Chinese population. This significantly reduced the scientific value of the paper and it would be more valuable if including analyses on the associations between various risk factors and the cardiometabolic multimorbidities. Response: We thank the Reviewer for this suggestion. Detailed information related to the data quality for the health information systems was described previously [BMJ Open 2018; 8(2):e01969]. We addressed the relatively important information, especially regarding the exposure and the outcomes, in the Method Section. E.g. "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." (page 7, line 86-89). "Death was confirmed by the death certificate in the health information system, as previously described.[Scientific reports 2016;6:31609] Diseases and deaths were classified according to the International Classification of Diseases, Tenth Revision (ICD-10)." (page 7, line 98-100). As stated in the protocol [BMJ Open 2018; 8(2):e019698], data completeness varies in CHERRY. We have now provided number and percentages of participants having at least one measurement of the covariates in this study in the Result Section (page 9, line 146-149).

We agree that CHERRY study is based on regional population in the developed area of China and the prevalence of cardiometabolic multimorbidity may not nationally representative. We have stated this in the study limitation (page 15, line 325-326). However, as mentioned in the Comment & Response of a recent JAMA paper [JAMA. 2017; 317(16):1689], even the most famous population-based cohort study with half a million Chinese participants - the China Kadoorie Biobank (CKB) - was not designed to be nationally representative due to the diversity of populations in China. Moreover, we believe that the rapid evolution of cardiometabolic multimorbidity, the association with mortality using longitudinal information of disease status, and therefore the need for a complementary strategy for primary and secondary prevention of cardiometabolic disease found in our study should be not only happened in this region but also happened in other places in China sooner or later in China. In this sense, our study may still have important implications.

As suggested, we now explore the extent to which conventional factors (BMI, smoking, education level and location) could explain the associations between cardiometabolic multimorbidity and mortality. HRs adjusted for these additional factors were calculated in people with full information on above factors. Results were shown in the new eTable 6. And we stated in the Results Section (page 11, line 214-217) "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)."

Reviewer 2

Overview: Zhang et al analyzed big data from 1,038,704 Chinese individuals from the CHERRY database. There were 22,750 deaths after a follow-up of 5.16 years. They showed that during follow-up the prevalence of multimorbidity (hypertension, diabetes and CVD) more than doubled, with CVD

contributing mostly to the risk of death. The study is of interest, the manuscript is well written, the analysis is sound and the conclusions are justified by the results.

Comments:

1.The results are somehow anticipated. It is known from previous studies that the prevalence of CVD and CVD risk factors is increasing in the Chinese population and that history of CVD is associated with increased risk of CVD and total death.
Response: We thank for the reviewer's comment. We agree that it is widely known that prevalence of individual disease in China is increasing. However, we believe that the key findings from our study using longitudinal information of the disease status, i.e. the rapid evolution of cardiometabolic multimorbidity and their associations with mortality, were still novel, especially in the Chinese population. History of CVD is associated with deaths. However, evidence on history of CVD with or without other accompanied cardiometabolic diseases was limited.

2.A lot of information is missing: type of CVD, risk factor control, medications, change of BMI, change of smoking status, etc.
Response: We thank for the reviewer's comment. We also now stated in the Results Section (page 9, line 149-154) that "The mean±SD age at baseline was 42.5±14.8 years (51.4% women). The mean BMI was 22.5±2.5 kg/m2. According to Asian-specific BMI cutoffs, 24.1% were overweight (23–25 kg/m2) and 13.9% were obese (BMI ≥25 kg/m2). At the last visit during follow-up, the mean BMI was 22.5±2.6 kg/m2; 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%." Regarding the history of CVD, we stated in page 10, line 170-173 "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. " Moreover, we now explore the extent to which conventional factors (BMI, smoking, education level and location) could explain the associations between cardiometabolic multimorbidity and mortality. HRs adjusted for these additional factors were calculated in people with full information on above factors. Results were shown in the new eTable 6. And we stated in the Results Section (page 11, line 214-217) 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)."

Reviewer 3

Overview: Cardiometabolic comorbidity data are critical developing appropriate interventions. The study described prevalence and hazard ratios of a population in an urban area using data from medical records. It gives insights on the evolution of cardiometabolic conditions.

Comments:

Page 2: Abstract: Results: Lines 37-40 and 46 – 50 describe the same results?
Response: Both lines 37-40 and 46 – 50 in Results described the HRs of cardiometabolic comorbidity for mortality. However, lines 37-40 reported HRs for mortality using baseline status of multimorbidity. Line 46-50 reported HRs using longitudinal status of multimorbidity (i.e. with repeat information on multimorbidity).

Page 3: Abstract: Last sentence: A complementary strategy of what is needed in the Chinese population?

Response: We thank for the reviewer's comment. We have now clarified in the Conclusions of Abstract (page 2) as "A complementary strategy for primary and secondary prevention of cardiometabolic diseases is needed in China."

Strengths and limitations: Remove "under real world circumstances"
Response: Revised as suggested.

Page 5, Line 34: The term of "evolution of multimorbidity" …Remove of after the word term.
Response: Revised as suggested.

Page 7: Line 78: "Participants is generally……" re-phrase
Response: We now described that "Follow-up in the health information system is generally continuous. CHERRY updates information for all cohort members annually from the health information system databases." (page 7, line 74-75)

Statistical Analysis
Indicate rather how descriptive and inferential anlaysis was done.
Response: We thank the Reviewer for this suggestion. In Methods section (page 8, line 103-107), we have now stated that for descriptive 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." For the inferential analysis, we described in the Method section as follows: "A Poisson regression model adjusted for sex was used to calculate mortality rates, adjusted for age 60 years." (page 8, line 111-112). "Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazard regression model…" (page 8, line 116-123).

Page 8: Line 110-113: Remove is part of results.
Response: Revised as suggested.

Page 8: Line 111: Re-phrase Numbers the corresponding percentages of participants who changed their cardiometabolic disease status within each 8 combination listed above were summarized.
Response: We have rephrased the sentence as "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." (page 8, line 104-107)

Page 8: Line 129: Re-phrase "We judged p values less than 0.05 significant".
Response: We have re-phrased as "We used Stata (version 14.0) for all data analyses, with a statistical significance level of P < 0.05."(page 9, line 130-132)

Page 9: Lines 148 – 150. Re-phrase "The estimated prevalence for the diagnosed cardiometabolic comorbidity was generally increased along with age and higher in women". It could as well be re-written "The estimated prevalence for the diagnosed cardiometabolic comorbidity increased with age and was higher in women than men".
Response: We thank the Reviewer for this suggestion. We have re-phased the sentence as suggested.

Page 9 and 10: Re-write the sentence, Line 160-163
Response: We have re-phrased the sentence as "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." (page 10, line 175-179)

Page 10: Re-write the sentence, Lines 165-166. Not advisable to start a sentence with a number.
Response: We have re-phrased the sentence as "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." (page 10, line 179-181)

Page 11: Line 217 rather than investigated write described……
Response: Revised as suggested.

Discussion
Page 12: Line 224-226. How do these results compare with other studies?
Response: We thank the Reviewer for this suggestion. We compared these results in the discussion section (page 13, Line 252-272). We stated that "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). [Geriatr Gerontol Int. 2015;15(1):1-10] 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. … 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). [JAMA 2015;314(1):52-60] 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. [JAMA. 2007; 298:1160-2] Previous studies in China and other countries have also shown that the prevalence of multimorbidity increased significantly with age.[BMC Med. 2014;12:188; Lancet. 2012;380:37-43] Older adults should therefore be a major population targeted for cardiometabolic multimorbidity prevention, considering population aging."

Page 13: Lines 249 – 260. How do these results compare with other studies?
Response: We thank the Reviewer for this suggestion. Regarding the association of multimorbidity with mortality, we compared results with other studies in page 14 line 306-317. Though our 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. In contrast, The results from the ERFC involving 91 cohort studies (mainly Western populations) estimated the HR for mortality was about 2 in participants with one cardiometabolic multimorbidity condition (type 2 diabetes, coronary heart disease, or 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. Detailed discussion was shown in page 14 line 306-317.

Page 14: Line 290-293: Is the conclusion from this study which is in an urban setting or from another study. A reference is needed to compare with studies in rural settings.
Response: This conclusion is from this study. Although Yinzhou District is a developed area in China, it has towns/villages located in the urban and rural areas respectively, which allowed us to investigate this heterogeneity. The conclusion were made according to the finding in the Results Section (page 11, line 199-201), where we illustrated that "HRs for cardiometabolic comorbidity were … higher in those living in urban areas (Supplementary eTable 4)."

eTable 3: Correct lase in the sentence: "Number of disorders at lase visit"
Response: Revised as suggested

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General Comments

English needs to be reviewed.
Response: The manuscript was edited throughout by a native-English-speaking expert provided by Edanz Editing China (https://www.edanzediting.com).

The discussion should be underpinned with comparison to results of studies elsewhere. The authors need to these comparisons.
Response: We have now provided additional discussion on the comparison with other studies in Discussion section. Please see the response to questions raised by reviewer #3.

Was the data complete for all the participants? If not, indicate the number and percentages of missing data points for each of the covariates and the methods used to address this. Was any multiple imputation done to complete the data?
Response: We have now provided number and percentages of participants having at least one measurement of the covariates in this study in the Result Section (page 9, line 146-149). We didn't use multiple imputation to complete the data of conventional factors including BMI, smoking and others. The primary analysis were only adjusted for age and sex, given the consideration that in the Emerging risk factor collaboration study [JAMA 2015;314(1):52-60] "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." (Page 16, line 333-336).