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Association between inequalities in human resources for health and all cause and cause specific mortality in 172 countries and territories, 1990-2019: observational study

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2023;381:e073043
http://dx.doi.org/10.1136/bmj-2022-073043

Accepted: 28 March 2023

ABSTRACT

OBJECTIVE

To explore inequalities in human resources for health (HRH) in relation to all cause and cause specific mortality globally in 1990-2019.

DESIGN

Observational study.

SETTING

172 countries and territories.

DATA SOURCES

Databases of the Global Burden of Disease Study 2019, United Nations Statistics, and Our World in Data.

MAIN OUTCOME MEASURES

The main outcome was age standardized all cause mortality per 100 000 population in relation to HRH density per 10 000 population, and secondary outcome was age standardized cause specific mortality. The Lorenz curve and the concentration index (CCI) were used to assess trends and inequalities in HRH.

RESULTS

Globally, the total HRH density per 10 000 population increased, from 56.0 in 1990 to 142.5 in 2019, whereas age standardized all cause mortality per 100 000 population decreased, from 995.5 in 1990 to 743.8 in 2019. The Lorenz curve lay below the equality line and CCI was 0.43 (P<0.05), indicating that the health workforce was more concentrated among countries and territories ranked high on the human development index. The CCI for HRH was stable, at about 0.42-0.43 between 1990 and 2001 and continued to decline (narrowed inequality), from 0.43 in 2001 to 0.38 in 2019 (P<0.001). In the multivariable generalized estimating equation model, a negative association was found between total HRH level and all cause mortality, with the highest levels of HRH as reference (low: incidence risk ratio 1.15, 95% confidence interval 1.00 to 1.32; middle: 1.14, 1.01 to 1.29; high: 1.18, 1.08 to 1.28). A negative association between total HRH density and mortality rate was more pronounced for some types of cause specific mortality, including neglected tropical diseases and malaria, enteric infections, maternal and neonatal disorders, and diabetes and kidney diseases. The risk of death was more likely to be higher in people from countries and territories with a lower density of doctors, dentistry staff, pharmaceutical staff, aides and emergency medical workers, optometrists, psychologists, personal care workers, physiotherapists, and radiographers.

CONCLUSIONS

Inequalities in HRH have been decreasing over the past 30 years globally but persist. All cause mortality and most types of cause specific mortality were relatively higher in countries and territories with a limited health workforce, especially for several specific HRH types among priority diseases. The findings highlight the importance of strengthening political commitment to develop equity oriented health workforce policies, expanding health financing, and implementing targeted measures to reduce deaths related to inadequate HRH to achieve universal health coverage by 2030.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Human resources for health (HRH), a range of occupations to promote or improve health, are of importance to achieve universal health coverage by 2030

Although several studies have analyzed the relation between HRH density and mortality rate, most focused on maternal mortality ratio and mortality rates in under-5s, infants, and neonates

Studies focusing on inequalities in total and specific HRH types and relations with cause specific mortality from a global perspective across three decades are scare

WHAT THIS STUDY ADDS

Inequalities in HRH have been decreasing globally over the past 30 years but persist

The negative association between total HRH density and mortality rate was statistically significant and more pronounced for some types of cause specific mortality

Countries and territories should refocus on the human resource pool of priority HRH cadres on the basis of leading cause specific mortality

Introduction

Human resources for health (HRH), a range of occupations designed to promote or improve human health, are of vital importance in the process of achieving universal health coverage by 2030.[1-3] In September 2015, the United Nations adopted a new development agenda, with 17 sustainable development goals replacing the millennium development goals, and sustainable development goal 3 focusing on a broad range of health goals.[4-6] One of the specific targets of sustainable development goal 3 is to substantially increase health financing and the recruitment, development, training, and retention of the health workforce in developing countries.[5] In July 2020, the World Health Organization, through its global strategy for HRH, further reaffirmed the vision

to accelerate progress towards achieving universal health coverage and the sustainable development goals by ensuring equitable access to health workers in strengthened health systems.[7] Global public health emergencies such as the covid-19 pandemic also present major challenges to the availability, equity, and future planning of HRH globally.[8]

HRH is one of the essential safeguards for health.[9] Practically, a shortage in HRH was the most conspicuous constraint on the lack of success of many countries to achieve the three health related millennium development goal targets—reducing child mortality, improving maternal health, and combat HIV/AIDS and other diseases.[10-14] Achieving universal health coverage depends not only on the availability of a sufficient number of qualified and motivated health workers but also on their equitable distribution.[13 15] The uneven distribution of health staff is a serious and longstanding global problem, especially for the imbalanced distribution across countries and territories.[16 17] One study found that the Americas, which comprises 37% of the global health workforce, has only 10% of the global burden of disease.[17] In contrast, sub-Saharan Africa has more than 24% of the global burden of disease but only 3% of the global health workforce.[17 18] Population mortality rates can be affected by factors both internal and external to the health workforce,[4 8 19 20] including productivity level, healthcare conditions, education level, social welfare policies, and natural disasters. An econometric study showed that higher density of a health workforce, particularly of total skilled health workers and nursing and midwifery staff, was substantially correlated with a lower maternal mortality ratio and mortality rates in under-5s, infants, and neonates, and the higher health workforce density was also significantly associated with lower excess covid-19 deaths per 100 000 population.[4] However, the association between the density of doctors and maternal mortality ratio and mortality rates in under-5s, infants, and neonates was inconsistent in several earlier studies.[21-25] Moreover, no significant results were identified in five cross country studies that investigated the associations between nurse density and maternal mortality ratio and mortality rate in under-5s and infants.[21-23 26 27] The inconsistent results of previous studies may have resulted from the methods, variables, and procedures used.[21-23 26 27]

Although several studies[4 21-27] have analyzed the relation between HRH and mortality rate, studies focusing on inequalities in HRH in association with cause specific mortality from a global perspective are scarce. To help contribute to the promotion of healthy lives and wellbeing and effective universal health coverage, we quantified the associations between HRH and all cause and cause specific mortality in 172 countries and territories representing most of WHO's member states. To provide baseline data for understanding the current distribution of HRH, we also explored the inequalities in HRH from 1990 to 2019.

Methods

Study design and data sources

We collected yearly data on total HRH, specific types of HRH, all cause mortality, and cause specific mortality from 1990 to 2019 at country level from the Global Burden of Disease Results (https://vizhub.healthdata.org/gbd-results/), a widely used database coordinated by the Institute for Health Metrics and Evaluation.[28] Based on the assessment criteria of data quality, to ensure rigor of the data we finally included 172 of the 204 countries and territories (see supplementary table S1). Data on demographic characteristics, socioeconomic status, and health services were obtained from United Nations Statistics (http://data.un.org/) and Our World in Data (https://ourworldindata.org/) to be used as covariates in our models (see supplementary methods for details).[29-31]

Human resources for health

HRH encompasses a range of occupations intended to promote or improve human health.[1-3] We extracted annual data for the densities of both total and specific types of HRH (per 10 000 population) from 1990 to 2019 by location from the Global Burden of Disease Study 2019 (see supplementary table S2).[32] After we had consolidated similar occupations, 16 health worker cadres remained (see supplementary table S4). Doctors, nursing and midwifery staff, dentistry staff, and pharmaceutical staff are highlighted in sustainable development goal 3.c.1.[2 33 34] The Global Burden of Disease Study produced modeled estimates for the missing data points (see supplementary table S3). Briefly, the Institute for Health Metrics and Evaluation systematically extracted data from WHO's Global Health Observatory and representative cross sectional surveys and censuses that sampled general working age populations (defined as ages 15-69) in which respondents self-reported employment status and current occupation.[32] Employment and occupation data for HRH in the Global Burden of Disease Study 2019 were mapped to the International Standard Classification of Occupations-88.[32 35] After the HRH cadres had been split and bias corrections performed, we applied spatiotemporal Gaussian process regression—a flexible three stage modeling approach—to model HRH densities from 1990 to 2019 for all of the countries and territories. This model is widely used in Global Burden of Disease studies, allowing the generation of full time series estimates with uncertainty intervals from data that are usually unevenly distributed in space and time.[35]

All cause and cause specific mortality

In this study we considered age standardized all cause mortality (per 100 000 population) as the primary outcome and 21 age standardized types of cause specific mortality as secondary outcomes (see supplementary table S5). The Global Burden of Disease cause of death database 2019 consists

doi: 10.1136/bmj-2022-073043 | BMJ 2023;381:e073043 | the bmj

of all available global data extracted from vital registration, verbal autopsy, registry, survey, police report, and surveillance systems (see supplementary table S6).[36-38] To enhance comparability, the Global Burden of Disease group mapped detailed causes (coded according to the international classification of diseases) and redistributed garbage codes to the Global Burden of Disease cause list (levels 1-4).[37] After several steps of data correction, we modeled processed data using standardized tools to generate estimates of mortality. Cause of Death Ensemble modeling (CODEm), a highly systematized tool with four families of statistical models, was the framework used to model most of the cause specific death rates in the Global Burden of Disease. We used DisMod-MR 2.1, negative binomial models, natural history models, sub-cause proportion models, and prevalence based models to model a subset of causes of death with unique epidemiology, large changes in reporting over time, or particularly limited data availability.[37] For all cause mortality, we mainly used spatiotemporal Gaussian process regression to synthesize data sources after correction for known biases and to estimate the mortality rate (see supplementary methods).[36 37 39]

Statistical analysis

We compared demographic information, socioeconomics, and health resources among 172 countries and territories within different levels of HRH (lowest, low, middle, high, and highest) using median and interquartile range. Estimated annual percentage change was calculated by fitting the regression line: $y=\alpha+\beta x+\varepsilon$, where β represents the annual change in ln(HRH density or mortality rate).[40] We calculated estimated annual percentage change as $100\times(e^{\beta}-1)$ to assess the temporal trend of the HRH density and mortality rate, along with corresponding 95% confidence intervals.[41-43] If annual percentage change estimates and 95% confidence intervals were both >0 (or both <0), we considered the corresponding rate to be in an upward (or downward) trend.

We applied the Lorenz curve and the concentration index (CCI) to indicate the unequal distribution among countries with different development levels based on the human development index. The greater the deviation of the Lorenz curve from the diagonal line, the more marked the inequality. CCI is defined as twice the area between the curve and the diagonal, which ranges from −1 to 1. A positive CCI value indicates that HRH is distributed in the group ranked

Table 1 | Characteristics of demographics, socioeconomic status, and health services by different levels of human resources for health in 172 countries and territories, 1990-2019. Values are median (interquartile range) unless stated otherwise

		HRH levels					
Characteristics	Total	Lowest	Low	Middle	High	Highest	P value*
Demographic							
Population density (people per km^2)	82.2 (35.3-181.0)	61.0 (34.7-134.1)	78.6 (34.6-143.2)	79.4 (34.3-158.9)	94.5 (46.1-169.6)	112.3 (23.5-258.3)	<0.001
Population living in urban areas (%)	58.5 (40.6-77.3)	31.6 (18.9-44.4)	45.5 (32.8-58.6)	58.1 (49.8-73.9)	68.9 (58.2-84.9)	82.4 (74.1-91.5)	<0.001
Average years of schooling (years)	8.0 (5.6-10.1)	3.4 (2.3-4.5)	6.5 (5.3-7.9)	8.2 (7.3-9.5)	9.3 (8.1-10.7)	11.2 (9.6-12.1)	<0.001
Sociodemographic index	0.6 (0.5-0.7)	0.3 (0.2-0.4)	0.5 (0.4-0.6)	0.6 (0.6-0.7)	0.7 (0.7-0.8)	0.8 (0.8-0.8)	<0.001
Socioeconomic status							
GDP per capita†	10 990.6 (4661.8-25 076.6)	2085.0 (1414.9-3476.7)	6242.4 (3965.8-8943.1)	11 424.6 (8725.5-14 712.0)	19 247.7 (13 532.2-29 694.6)	40 414.4 (30 046.8-51 875.3)	<0.001
Human development index	0.7 (0.6-0.8)	0.4 (0.4-0.5)	0.6 (0.6-0.7)	0.7 (0.7-0.7)	0.8 (0.7-0.8)	0.9 (0.8-0.9)	<0.001
HRH (workers per 10 000 population)							
Total	89.7 (38.4-186.9)	21.0 (16.0-25.7)	46.1 (38.4-54.3)	89.7 (75.9-106.3)	163.4 (145.1-186.9)	338.1 (274.5-442.1)	<0.001
Cadres:							
Doctors	11.8 (4.6-23.3)	1.8 (1.0-3.8)	6.3 (3.7-9.1)	12.3 (7.8-17.4)	18.8 (13.4-26.8)	32.5 (25.7-39.8)	<0.001
Nursing and midwifery staff	33.0 (14.4-62.2)	8.2 (5.5-11.3)	18.9 (13.9-24.6)	33.8 (23.3-43.8)	56.0 (46.5-68.0)	108.9 (81.7-140.8)	<0.001
Dentistry staff	4.2 (0.9-9.5)	0.2 (0.1-0.4)	1.3 (0.7-2.6)	4.5 (2.3-6.8)	8.5 (5.2-10.7)	12.5 (9.7-16.3)	<0.001
Pharmaceutical staff	4.4 (1.6-10.1)	0.6 (0.4-1.4)	2.3 (1.2-3.4)	4.4 (2.5-6.4)	8.0 (5.2-11.8)	14.4 (10.4-18.4)	<0.001
Medical assistants and CHWs	2.5 (1.2-5.5)	1.2 (0.8-1.6)	1.6 (0.7-2.1)	2.5 (1.1-4.0)	4.3 (3.0-7.7)	8.1 (5.2-12.9)	<0.001
Aides and emergency medical workers	6.7 (2.1-25.2)	1.3 (0.7-2.2)	2.4 (1.3-4.2)	6.5 (3.7-10.5)	19.9 (13.2-28.4)	69.2 (39.8-107.6)	<0.001
Medical laboratory technicians	2.3 (0.8-5.0)	0.3 (0.2-0.6)	1.1 (0.6-1.8)	2.4 (1.6-3.4)	4.0 (2.9-6.1)	8.9 (5.2-12.2)	<0.001
Dietitians and nutritionists	1.0 (0.2-2.7)	0.1 (0.0-0.2)	0.4 (0.2-0.8)	1.1 (0.6-1.9)	2.3 (1.3-3.7)	3.8 (2.5-6.4)	<0.001
Optometrists	0.5 (0.1-2.1)	0.1 (0.0-0.1)	0.2 (0.1-0.3)	0.5 (0.2-1.2)	1.5 (0.8-2.8)	3.5 (2.3-5.0)	<0.001
Audiologists and counsellors	1.7 (0.6-4.3)	0.3 (0.1-0.8)	0.7 (0.3-1.5)	1.8 (1.0-2.9)	3.9 (2.4-5.9)	6.4 (4.3-9.4)	<0.001
Psychologists	2.2 (0.4-5.8)	0.2 (0.1-0.3)	0.6 (0.3-1.1)	2.3 (1.3-3.7)	4.8 (3.4-7.1)	9.5 (6.8-13.5)	<0.001
Environmental health officers	2.1 (0.6-4.4)	0.5 (0.3-0.7)	1.0 (0.5-2.0)	2.8 (1.0-4.4)	3.7 (1.9-6.5)	4.6 (3.4-7.3)	<0.001
Personal care workers	2.8 (0.7-9.6)	0.3 (0.1-0.8)	1.1 (0.4-2.4)	2.4 (1.1-4.7)	6.5 (3.8-11.5)	20.7 (11.3-32.7)	<0.001
Traditional and complementary medicine practitioners	1.4 (0.6-2.5)	1.6 (0.6-2.9)	1.1 (0.4-2.0)	1.0 (0.5-1.7)	1.4 (0.7-2.3)	2.5 (1.3-4.7)	<0.001
Physiotherapists	2.8 (0.4-7.4)	0.1 (0.1-0.3)	0.7 (0.3-1.9)	3.1 (1.5-5.4)	5.6 (3.3-8.8)	11.5 (7.8-18.1)	<0.001
Radiographers	0.9 (0.3-2.7)	0.2 (0.1-0.3)	0.4 (0.2-0.7)	0.8 (0.4-1.3)	1.9 (1.2-3.3)	5.4 (3.6-7.9)	<0.001

CHWs=community health workers; GDP=gross domestic product; HRH=human resources for health.
All P values <0.05.
*Test for trends for different HRH levels for demographic and socioeconomic characteristics, and for HRH variables for 1990 to 2019.
†Constant 2017 international $.

Table 2 | Trends in human resources for health density stratified by cadre in 172 countries and territories, 1990-2019. Values are median (interquartile range) unless stated otherwise

HRH (workers per 10 000 population)	HRH density		EAPC (%, 95% CI)	P value*
	1990	2019		
Total	56.0 (25.0-127.1)	142.5 (58.5-277.5)	2.9 (2.5 to 3.2)	<0.001
Cadres:				
Doctors	8.3 (3.4-17.2)	17.4 (7.5-30.7)	2.4 (2.0 to 2.8)	<0.001
Nursing and midwifery staff	21.6 (9.6-49.2)	49.3 (22.3-79.0)	2.2 (1.9 to 2.6)	<0.001
Dentistry staff	2.5 (0.5-6.0)	6.5 (2.0-12.0)	3.2 (2.6 to 3.7)	<0.001
Pharmaceutical staff	2.5 (1.0-6.3)	7.0 (2.7-15.1)	3.2 (2.8 to 3.5)	<0.001
Medical assistants and CHWs	1.7 (0.9-4.1)	3.7 (1.8-7.8)	2.6 (2.3 to 2.9)	<0.001
Aides and emergency medical workers	3.8 (1.2-17.3)	11.5 (3.8-41.7)	4.3 (3.8 to 4.8)	<0.001
Medical laboratory technicians	1.2 (0.4-2.8)	3.6 (1.5-7.0)	3.9 (3.5 to 4.3)	<0.001
Dietitians and nutritionists	0.6 (0.1-1.6)	2.0 (0.5-3.8)	4.2 (3.7 to 4.7)	<0.001
Optometrists	0.2 (0.0-1.1)	1.1 (0.3-3.7)	5.3 (4.8 to 5.9)	<0.001
Audiologists and counsellors	1.0 (0.4-2.7)	3.0 (1.0-6.5)	3.2 (2.8 to 3.7)	<0.001
Psychologists	1.2 (0.2-3.2)	4.3 (0.9-9.3)	4.5 (4.0 to 5.1)	<0.001
Environmental health officers	1.7 (0.5-3.5)	3.0 (1.0-5.5)	2.5 (2.1 to 2.9)	<0.001
Personal care workers	1.3 (0.3-4.4)	5.9 (1.7-15.6)	5.0 (4.4 to 5.6)	<0.001
Traditional and complementary medicine practitioners	1.2 (0.5-2.2)	1.8 (0.9-3.0)	1.5 (1.2 to 1.8)	<0.001
Physiotherapists	1.5 (0.2-4.7)	5.7 (0.9-11.0)	4.4 (3.9 to 5.0)	<0.001
Radiographers	0.4 (0.2-1.5)	1.5 (0.5-4.5)	3.8 (3.4 to 4.3)	<0.001

CI=confidence interval; CHW=community health worker; EAPC=estimated annual percentage change; HRH=human resources for health.
*P for trend <0.05.

higher on the human development index, whereas a negative value indicates the opposite. The closer to 0 the CCI is, the more equitable is the allocation of resources.[44] To assess the association between HRH (total and 16 types) and mortality rates (all cause and 21 cause specific), we applied the generalized estimating equation model, a widely used linear model for longitudinal data analysis with repeated measures over time.[45] The generalized estimating equation model used a gamma distribution and log-link function to control for the skewed nature of mortality. The dependent variable refers to ln(age standardized mortality rate). In the univariable model, after controlling for the effect of time, we explored the association between HRH and mortality rates using crude incidence risk ratios and corresponding 95% confidence intervals. In multivariable models, we controlled for year, population density, percentage of the population living in urban areas, average years of schooling, gross domestic product per capita, and ranking on the human development index. To test the robustness of the results, in sensitivity analyses we replaced the human development index with the socioeconomic index. STATA version 13.0 and SPSS version 23.0 were used in this study, and statistical significance was attributed to two sided P values <0.05. For more details on the statistical analysis, see the methods section in the supplementary file.

Patient and public involvement

Being involved in the Global Burden of Disease 2019 and other open databases rather than directly speaking to patients inspired this research. Although no patient was directly involved in this study, members of the public read our manuscript, and all agreed on the specific findings of this study.

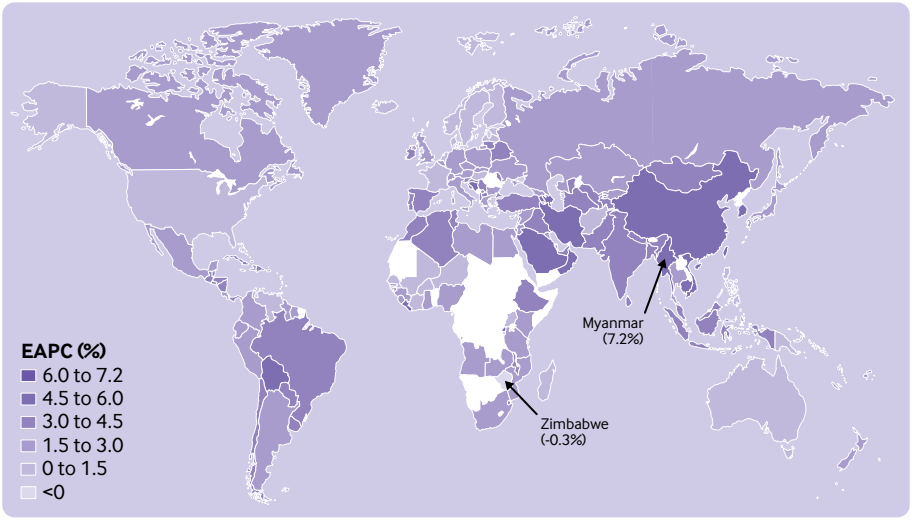

Fig 1 | Estimated annual percentage change (EAPC) in human resources for health per 10 000 population in 172 countries and territories, 1990-2019

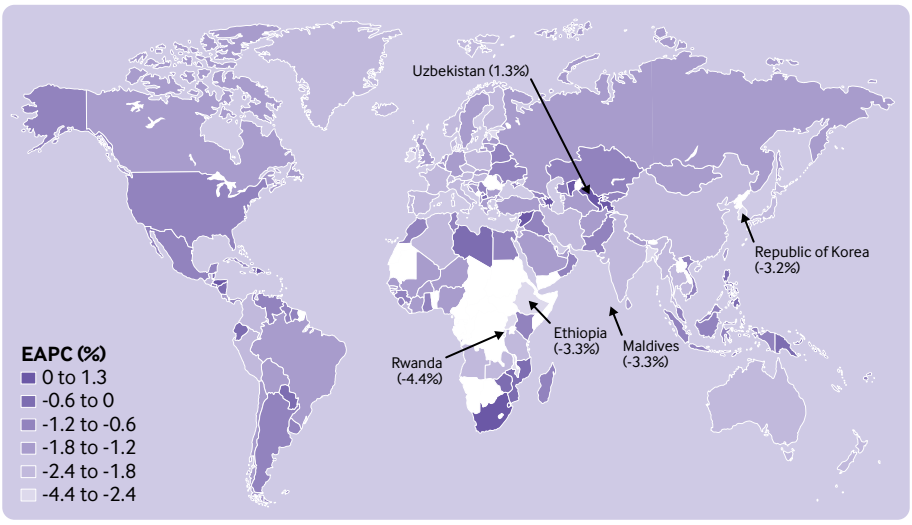

Fig 2 | Estimated annual percentage change (EAPC) in all cause mortality per 100 000 population in 172 countries and territories, 1990-2019

Results

Basic characteristics and different levels of HRH

Countries and territories with higher levels of HRH were likely to have higher population density, a higher percentage of the population living in urban areas, more average years of schooling, and a higher socioeconomic index (all P<0.05) (table 1). For indicators denoting socioeconomic status, gross domestic product per capita and the human development index were also positively changed with the increase of total health workforce. In addition, the total median density of HRH between 1990 and 2019 was 89.7 (interquartile range (IQR) 38.4-186.9) workers per 10 000 population, ranging from 21.0 to 338.1 workers per 10 000 population in countries with different HRH levels. Similar distributions were seen in all 16 HRH cadres.

Trends and inequalities in HRH among 172 countries and territories

Globally, total HRH density increased from 56.0 per 10 000 population in 1990 to 142.5 per 10 000 population in 2019, with an estimated annual percentage change of 2.9% (95% confidence interval 2.5% to 3.2%). A positive estimated annual percentage change was observed in each cadre, ranging from 1.5% for traditional and complementary medicine practitioners to 5.3% for optometrists (table 2). Among 172 countries and territories, the total HRH density in 2019 was distributed unevenly—Sweden had the highest access to HRH per capita (696.1 workers per 10 000 population), whereas Ethiopia and Guinea had less than one ninth of the global HRH level, with 13.9 and 15.1 workers per 10 000 population, respectively (see supplementary table S7). Except for Zimbabwe (−0.3%, −0.6% to 0%), all countries had a positive estimated annual percentage change (P<0.05; fig 1, also see fig 2 for all cause mortality estimates per 100 000 population) and supplementary table S7). Myanmar had the highest estimated annual percentage change in HRH density (7.2%, 6.9% to 7.5%). Supplementary table S8 and supplementary figure S2 display the densities and estimated annual percentage changes in 16 HRH cadres in 172 countries and territories.

The Lorenz curve of health worker density lay below the equality line, with a positive CCI of 0.43 (P<0.05), indicating that the health workforce was more concentrated among countries and territories that ranked high on the human development index (fig 3). Supplementary figure S1 shows the Lorenz curve of all 16 cadres of HRH. The CCI for HRH was stable at about 0.42-0.43 between 1990 and 2001 and continued to decline (narrowed inequality), from 0.43 in 2001 to 0.38 in 2019 (P<0.001, fig 4, supplementary table S9). The CCI of four HRH cadres highlighted in sustainable development goal 3c.1—doctors, nursing and midwifery staff, dentistry staff, and pharmaceutical staff were 0.37, 0.38, 0.43, and 0.41, respectively (P<0.001, supplementary table S10).

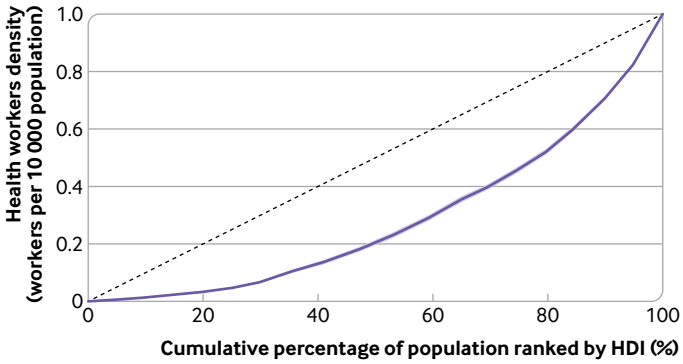

Fig 3 | Lorenz curve of health worker density for human resources for health among 172 countries and territories, 1990-2019. HDI=human development index. Diagonal broken line represents equity line. Shaded area represents 95% confidence interval

Disparities in mortality among 172 countries and territories

The all cause age standardized mortality rate decreased from 995.5 (IQR 790.9-1317.0) per 100 000

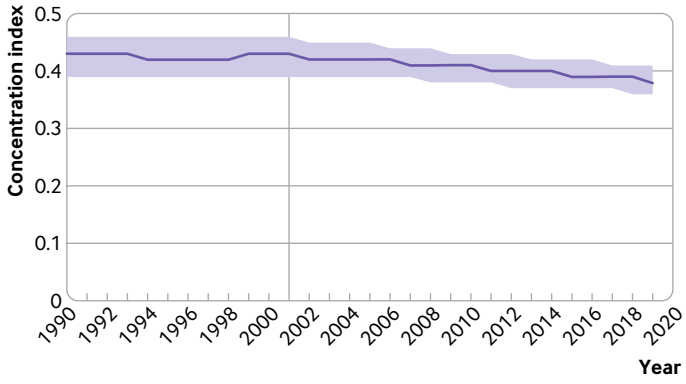

Fig 4 | Trends in concentration index for human resources for health, among 172 countries and territories, 1990-2019. Shaded area represents 95% confidence interval

population in 1990 to 743.8 (539.0-990.9) per 100 000 population in 2019, with an estimated annual percentage change of −1.3% (95% confidence interval −1.4% to −1.2%) (table 3). The age standardized mortality rate in 2019 was highest in the Solomon Islands (1919.9) and lowest in Singapore (324.1) and Japan (323.3) (see supplementary table S11), The estimated annual percentage change differed, from the highest in Uzbekistan (1.3%, 0.8% to 1.8%) to the lowest in the Maldives (−3.3%, −3.5% to −3.0%), Ethiopia (−3.3%, −3.5% to −3.1%), and Rwanda (−4.4%, −5.7% to −3.1%) (fig 2 and supplementary table S11). For the 21 types of cause specific mortality, the number of deaths per 100 000 population declined from 1990 to 2019 for most of the causes, except for deaths due to neurological disorders, mental disorders, skin and subcutaneous diseases, and musculoskeletal disorders (table 3). According to the results shown in supplementary table S12, the mortality rate for HIV/AIDS and sexually transmitted infections increased from 2.0 (95% confidence interval 0.7 to 7.6) per 100 000 population in 1990 to 3.6 (0.7 to 19.1) per 100 000 population in 2000, but then decreased steadily to 3.4 (0.6 to 11.5) per 100 000 population in 2019. The mortality rate increased before 2000 (estimated annual percentage change 7.5%, 95% confidence interval 4.0% to 11.2%) and then declined after 2010 (−2.7%, −5.9% to 0.5%).

Results using generalized estimating equation model

In the multivariable generalized estimating equation model, a negative association was observed between total HRH density and all cause mortality, with the highest HRH levels as reference group (low: adjusted incidence risk ratio 1.15, 95% confidence interval 1.00 to 1.32; middle: 1.14, 1.01 to 1.29; high: 1.18, 1.08 to 1.28) (fig 5, fig 6, and supplementary table S13). The increase in human development index (0.06, 95% confidence interval 0.03 to 0.10) may also be related to the decreased mortality (supplementary table S13). Compared with the Solomon Islands (HRH 42.0, age standardized mortality rate 1919.9), some countries had a very low density of HRH in 2019 but lower all cause mortality, such as Ethiopia (18.2, 993.5), Morocco (32.3, 851.5), and Palestine (34.9, 796.6) (see supplementary figure S19).

In most disease models, negative associations were found between total HRH density and particular types of cause specific mortality, except for HIV/AIDS and sexually transmitted infections, neoplasms,

Table 3 | Trends for all cause and cause specific mortality in 172 countries and territories, 1990-2019

Mortality per 100 000 population	Age standardized mortality rate (IQR)		EAPC (%, 95% CI)	P value
	1990	2019		
All cause	995.5 (790.9-1317.0)	743.8 (539.0-990.9)	−1.3 (−1.4 to −1.2)	<0.001*
Cause specific:				
HIV/AIDS and sexually transmitted infections	2.0 (0.7-7.6)	3.4 (0.6-11.5)	0.3 (−0.4 to 1.0)	0.37
Respiratory infections and tuberculosis	53.8 (31.5-152.4)	30.0 (17.7-77.8)	−2.2 (−2.5 to −1.9)	<0.001*
Enteric infections	9.6 (1.2-45.5)	2.6 (1.0-12.9)	−2.9 (−3.6 to −2.3)	<0.001*
Neglected tropical diseases and malaria	0.7 (0.1-7.4)	0.3 (0.1-2.2)	−3.2 (−4.1 to −2.3)	<0.001*
Other infectious diseases	8.7 (3.0-29.8)	2.7 (1.4-8.8)	−3.7 (−4.1 to −3.3)	<0.001*
Maternal and neonatal disorders	29.7 (13.1-53.0)	10.7 (4.3-25.3)	−2.9 (−3.2 to −2.6)	<0.001*
Nutritional deficiencies	2.9 (0.7-15.8)	1.3 (0.3-4.6)	−3.2 (−3.7 to −2.6)	<0.001*
Neoplasms	138.1 (111.2-164.6)	126.5 (109.2-147.2)	−0.2 (−0.3 to −0.1)	<0.001*
Cardiovascular diseases	346.6 (282.5-466.8)	257.9 (173.5-338.4)	−1.4 (−1.6 to −1.3)	<0.001*
Chronic respiratory diseases	43.3 (28.3-66.6)	28.9 (20.3-44.4)	−1.5 (−1.6 to −1.3)	<0.001*
Digestive diseases	40.8 (29.7-68.0)	32.3 (22.1-52.3)	−1.1 (−1.3 to −0.9)	<0.001*
Neurological disorders	31.0 (28.8-33.2)	31.5 (29.7-33.6)	0.1 (0.0 to 0.1)	<0.001*
Mental disorders	0.001 (0.000-0.002)	0.001 (0.000-0.003)	1.6 (1.1 to 2.0)	<0.001*
Substance use disorders	2.2 (1.4-4.2)	2.1 (1.4-4.6)	−0.3 (−0.6 to 0.0)	0.07
Diabetes and kidney diseases	50.2 (24.7-76.4)	54.0 (24.1-82.4)	0.2 (−0.1 to 0.4)	0.18
Skin and subcutaneous diseases	1.5 (0.4-2.4)	1.7 (0.5-2.6)	0.6 (0.2 to 1.0)	0.002*
Musculoskeletal disorders	1.1 (0.6-1.7)	1.1 (0.8-1.8)	0.4 (0.2 to 0.7)	<0.001*
Other non-communicable diseases	19.5 (14.6-26.3)	14.5 (10.3-20.8)	−1.1 (−1.2 to −0.9)	<0.001*
Transport injuries	22.4 (16.7-30.1)	14.2 (8.5-20.4)	−2.0 (−2.2 to −1.9)	<0.001*
Unintentional injuries	31.1 (21.3-40.6)	18.5 (13.2-27.6)	−1.7 (−1.8 to −1.5)	<0.001*
Self-harm and interpersonal violence	18.9 (12.7-27.7)	14.2 (9.4-23.1)	−1.1 (−1.4 to −0.9)	<0.001*

CI=confidence interval; EAPC=estimated annual percentage change; IQR=interquartile range.
Mortality rate shown as median (IQR).
*P value for trends <0.05.

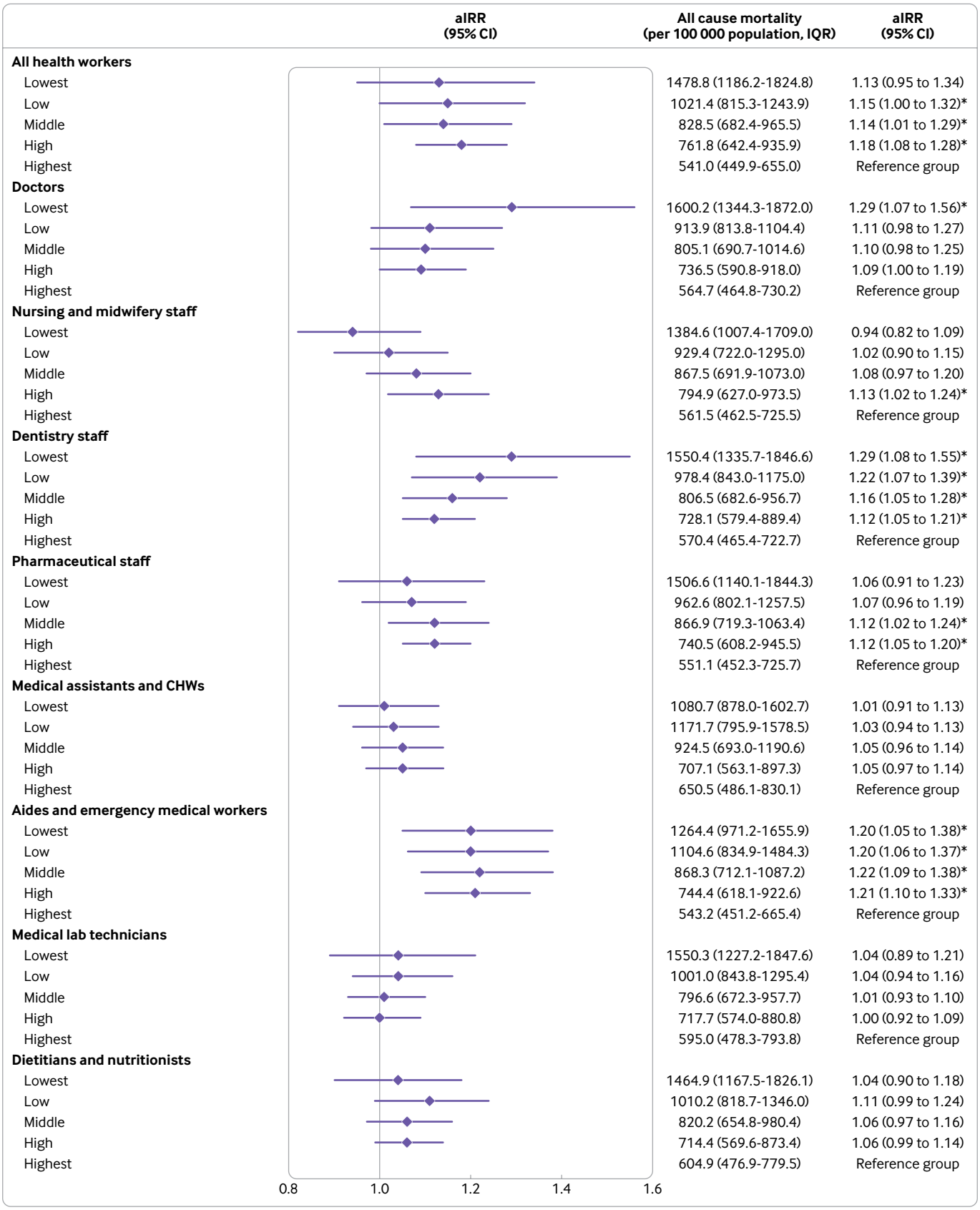

Fig 5 | Multivariable generalized estimating equation models showing association between human resources for health and all cause mortality for all health workers and eight of 16 cadres (see fig 6 for the other eight cadres in the current study) in 172 countries and territories, 1990-2019. Multivariable models were adjusted for health worker densities, year, population density, percentage of population living in urban areas, average years of schooling, gross domestic product per capita, and ranking on the human development index. aIRR=adjusted incidence risk ratio; CHWs=community health workers; CI=confidence interval; IQR=interquartile range. *P<0.05

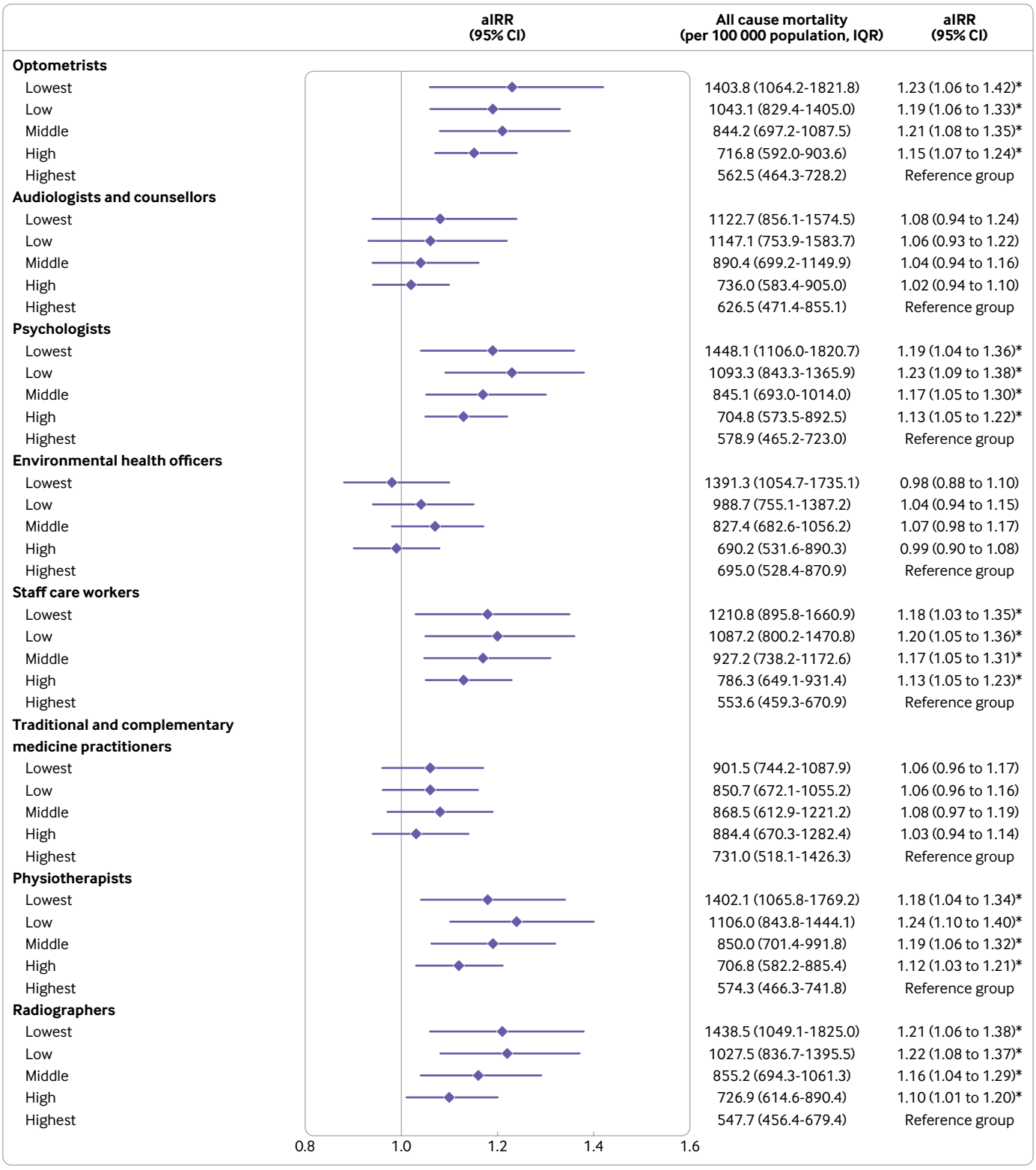

Fig 6 | Multivariable generalized estimating equation models showing association between human resources for health and all cause mortality for eight of 16 cadres (see fig 5 for the other eight cadres in the current study) in 172 countries and territories, 1990-2019. Multivariable models were adjusted for health worker densities, year, population density, percentage of population living in urban areas, average years of schooling, gross domestic product per capita, and ranking on the human development index. aIRR=adjusted incidence risk ratio; CI=confidence interval; IQR=interquartile range. *P<0.05

mental disorders, substance use disorders, and musculoskeletal disorders (fig 7 and fig 8). The risk of death due to enteric infections (lowest: adjusted incidence risk ratio 5.52, 95% confidence interval 2.95 to 10.33; low: 4.84, 3.15 to 7.43), neglected tropical diseases and malaria (lowest: 4.19, 1.81 to 9.74; low:

doi: 10.1136/bmj-2022-073043 | *BMJ* 2023;381:e073043 | the bmj

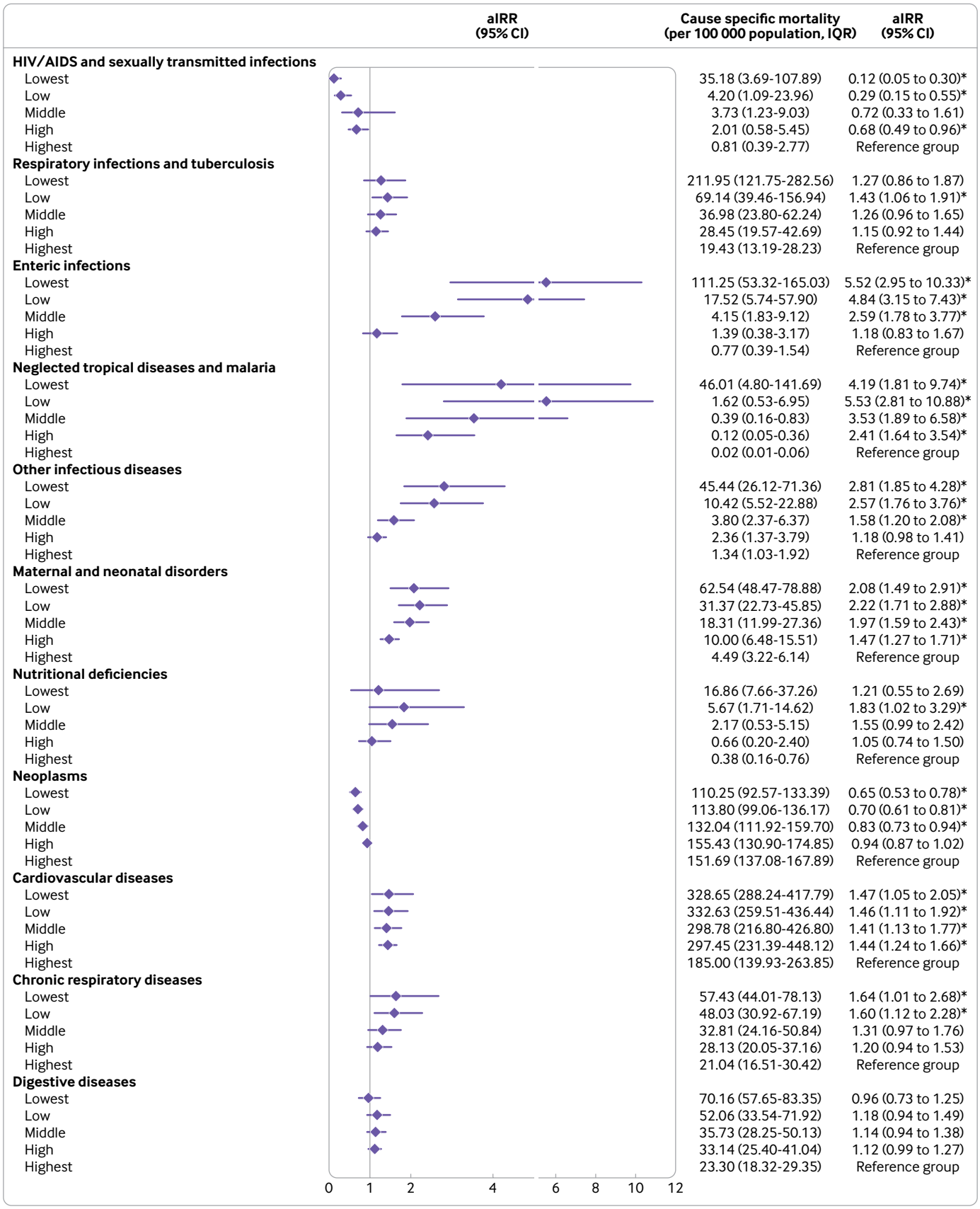

Fig 7 | Multivariable generalized estimating equation models showing association between human resources for health and 11 types of cause specific mortality (see figure 8 for other 10 types in the current study) in 172 countries and territories, 1990-2019. Models were adjusted for health worker densities, year, population density, percentage of population living in urban areas, average years of schooling, gross domestic product per capita, and ranking on human development index. aIRR=adjusted incidence risk ratio; CI=confidence interval; IQR=interquartile range. *P<0.05

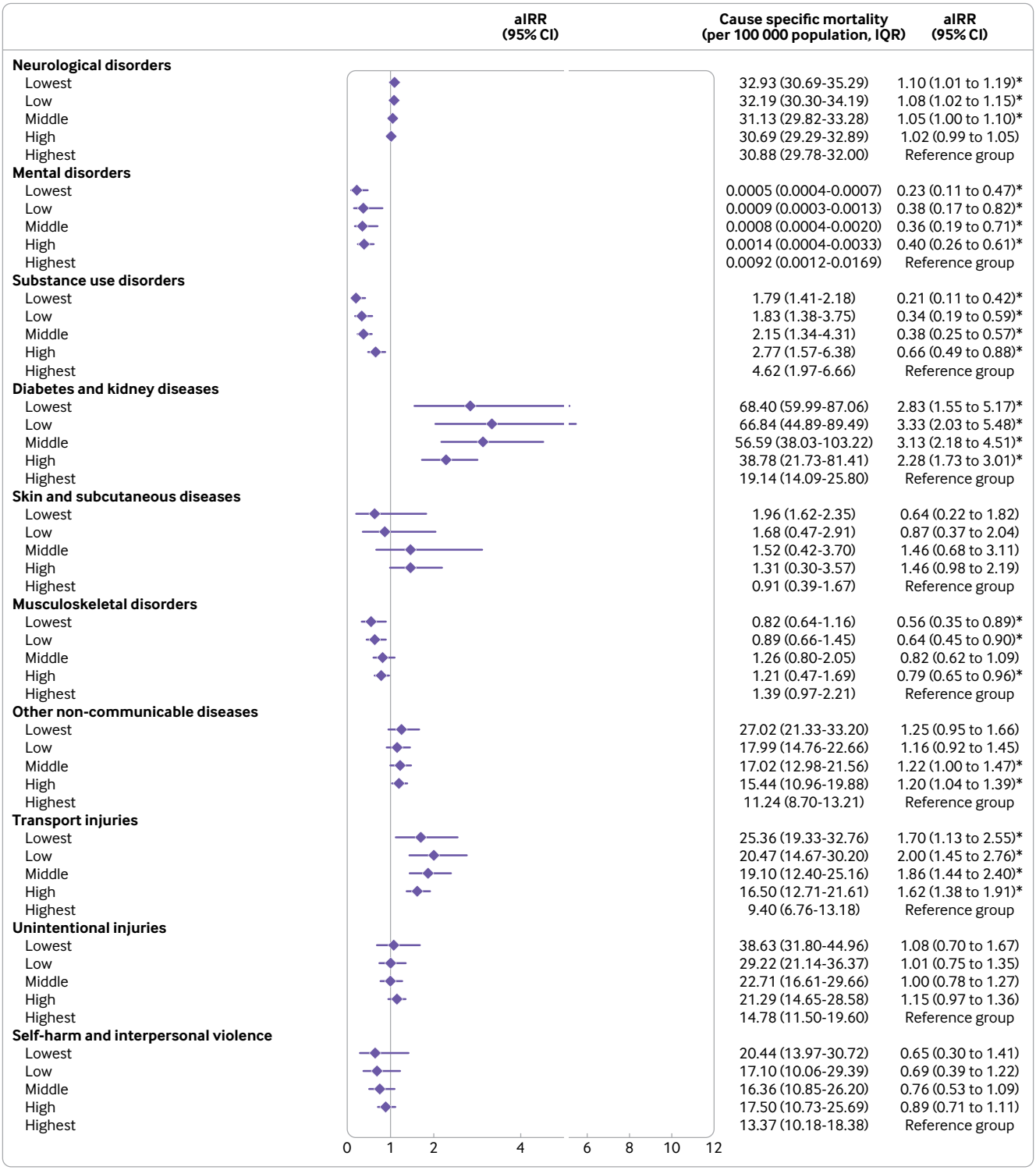

Fig 8 | Multivariable generalized estimating equation models showing associations between human resources for health and 10 types of cause specific mortality (see figure 7 for other 11 types in the current study) in 172 countries and territories, 1990-2019. Models were adjusted for health worker densities, year, population density, percentage of population living in urban areas, average years of schooling, gross domestic product per capita, and human development index. aIRR=adjusted incidence risk ratio; CI=confidence interval; IQR=interquartile range. *P<0.05

5.53, 2.81 to 10.88), diabetes and kidney diseases (lowest: 2.83, 1.55 to 5.17; low: 3.33, 2.03 to 5.48), and maternal and neonatal disorders (lowest: 2.08, 1.49 to 2.91; low: 2.22, 1.71 to 2.88) was much higher in areas with low or the lowest HRH density than in areas with the highest HRH density (fig 7 and fig 8).

Subgroup analysis: specific types of HRH density and mortality

Figure 5 and figure 6 show the association between 16 cadres of HRH and all cause mortality, with the highest group as reference. People in countries and territories with a lower density of doctors, dentistry

staff, pharmaceutical staff, aides and emergency medical workers, optometrists, psychologists, personal care workers, physiotherapists, and radiographers appeared to be at higher risk of death. The associations between both total and specific HRH density and all cause mortality were similar in sensitivity analysis (see supplementary table S15).

When both HRH density and mortality were divided into specific groups, strong negative associations were found for most of the 16 cadres of HRH and cause specific mortality (see supplementary figures S3-S18). The risk of death due to HIV/AIDS and sexually transmitted infections significantly increased in areas with a lower per capita number of doctors (lowest: adjusted incidence risk ratio 18.01, 6.14 to 52.89; low: 5.19, 10.32 to 20.45), dentistry staff (lowest: 6.02, 2.10 to 17.28), and pharmaceutical staff (lowest: 3.49, 1.31 to 9.25; low: 3.24, 1.68 to 6.27; middle: 3.97, 1.09 to 3.15). The association between cadres of doctors, nursing and midwifery staff, pharmaceutical staff, dietitians and nutritionists, and medical laboratory technicians and a reduction in mortality from neglected tropical diseases and malaria was noticeable. When general medical staff were excluded from analysis, a lower density of dentistry staff, aides and emergency medical workers, psychologists, and personal care workers was associated with increased maternal and neonatal disease related mortality. In addition, the increase in mortality from diabetes and kidney diseases seemed to be influenced to some extent by inadequate numbers of optometrists, psychologists, personal care workers, and radiographers.

Discussion

Integrating data from the Global Burden of Disease database, we found inequalities in the distribution of HRH and that this inequality was concentrated in countries and territories with a higher ranking on the human development index. Inequalities have also decreased over time. Using the highest HRH rank as reference, we found a negative association between total HRH density and all cause mortality and most types of cause specific mortality in generalized estimating equation models. Results from subgroup analysis indicated a strong association between lower HRH density and higher cause specific mortality across different HRH cadres and most of the cause specific mortality investigated in the current study. These findings outline the current inequalities in HRH globally and the potential risk of mortality. Countries and territories are supposed to improve HRH based on national conditions, especially for particular cadres of HRH, contributing to achievement of universal health coverage by 2030.

Inequalities and current status of HRH

Inequity in HRH has been a longstanding critical international issue.[16 17 46] In the current study, we found that the health workforce tended to be concentrated in countries and territories that ranked higher on the human development index. Inadequate health financing, low education levels, lack of employment opportunities, war, and violence against health workers are possible factors contributing to this inequality.[47-50] The Global Burden of Disease super regions of sub-Saharan Africa, South Asia, North Africa, and the Middle East were the most prominent regions with low density HRH, confirming our findings.[2] A reasonable population capacity is favorable to promoting sustainable development. Since the overall population carrying capacity varies between countries, without clear and appropriate fertility planning and economic development schemes, countries with an excessively large population may have collapsed economies, healthcare, education, and other sectors.[51-54] According to our findings, Myanmar had the highest estimated annual percentage change at 7.2% in HRH density—the governing party had accelerated the systemic strengthening of healthcare with economic and non-economic incentives, including social recognition and career development.[55 56] Despite the high estimated annual percentage change in Myanmar, the HRH density remained low, at 58.40 per 10 000 population. Many developing countries experience structural vulnerabilities and loss of HRH, such as Nigeria.[57 58] Challenges in national development priorities often divert scarce resources from the health sector.[47-50 57 58] Zimbabwe was the only country with negative HRH growth, multiple inflationary financial crises, and an unstable regime, and its deployment decisions on healthcare were elusive, even during the apparent losses to the health workforce. Although this inequality in health workforce exists, the gap has been narrowing since the turn of the century, which may be due in part to the effective implementation of both millennium development goals and sustainable development goals.[4-6]

Changes in all cause and cause specific mortality

In the current study, the large differences in mortality among countries might be related to inequalities in HRH, economic development, social security, medical insurance system, lifestyle, and dietary habits.[59-66] Compared with the Solomon Islands, some countries, such as Ethiopia and Palestine, had a very low HRH density in 2019 but all cause mortality was not high. Ethiopia is the second most populous country in Africa, and it has the fastest growing African economy in recent decades.[67] Life expectancy in Ethiopia increased from 52 years in 2000 to 66 years in 2019, and the rate of infant mortality reduced by more than 50%.[68] Most of the health related millennium development goals have been achieved in Ethiopia and are considered to be attributed to a comprehensive approach to health development, including health financing and other socioeconomic systems.[69 70] Palestine is a refugee area that has received high levels of aid and a considerable amount of charitable resources per capita.[71] Even the poorest countries seem to have achieved important reductions in all cause mortality by implementing these multi-tiered strategies.[70]

In addition, mortality rates for several diseases in our study were increasing, the most notable being for mental disorders, which had the highest estimated annual percentage change at 1.6%, although the mortality rate was still low at 0.001 per 100 000 population. Psychological problems are becoming more common as a result of heightened social pressures, and diagnostic capabilities have improved with advances in neuroscience and psychiatric care.[72-74] The mortality rate for HIV/AIDS and sexually transmitted infections increased from 2.0 to 3.4 per 100 000 population between 1990 and 2019; however, since 2010 the number of patients with newly diagnosed HIV has decreased by 32% (mostly among children, −52%), and AIDS related deaths have decreased by 68%, after peaking at two million in 2004, as a result of global initiatives to combat it over the past decades.[75-79] Nonetheless, the challenge to control sexually transmitted infections is big.[80] The estimated annual percentage change in mortality rate due to diabetes and kidney disease was 0.2%, in line with the findings of a previous study.[81] Another study indicated that the global burden of diabetes has increased statistically significantly since 1990, and that it continues to rise.[82] For skin and subcutaneous diseases (estimated annual percentage change 0.6%), many factors could explain the prevalence of skin diseases, including local weather, climate change, and diet. Differences might also be related to changes in dermatologist density and health insurance coverage.[83] The burden of musculoskeletal disorders may be underestimated, particularly because of population growth, ageing, and other associated risk factors (eg, obesity, injuries, and sedentary lifestyles).[84 85]

HRH and mortality

The negative association between total HRH density and mortality rates was statistically significant and more pronounced for some types of cause specific mortality. Neoplasms, mental disorders, substance use disorders, musculoskeletal disorders, self-harm, and interpersonal violence were, however, found to be positively related to total HRH density. Previous studies and statements of the World Cancer Research Fund International claimed that the age standardized mortality rate of neoplasms appeared to be higher in more developed countries, because of ageing and inappropriate lifestyle behaviors.[86-88] These risk factors are also becoming prevalent in low to middle income countries.[86] Mental disorders and their detection are of greater concern in more developed countries with high HRH density. The relative risk of all violent outcomes typically increased twofold to fourfold in most patients with a diagnosis of mental disorders compared with those without, potentially explaining the association between self-harm and interpersonal violence mortality and HRH density.[89] The higher mortality of substance use disorders in countries with a high HRH density was attributed to high rates of illicit drug use in high income countries.[90] Substance use disorders are also associated with an increased risk of death by suicide.[91] Most painful musculoskeletal disorders worsen with age, and most are related to multiple non-communicable diseases associated with musculoskeletal pain. The increasing incidence of reduced physical activity, non-communicable diseases, and age related diseases may explain the higher mortality rate for musculoskeletal disorders in countries with a high HRH density.[85]

The anomalous association between total HRH density and mortality from HIV/AIDS and sexually transmitted infections appeared challenging to elucidate, so we disaggregated the HRH density into 16 cadres to refine our results. Shortages of doctors, dentistry staff, and pharmaceutical staff were more likely to be associated with higher mortality (see supplementary figures S3, S5, and S6). The presence of oral lesions is regarded as an important sign in the diagnosis of AIDS.[92 93] More than one third of people with AIDS have oral lesions, and the average prevalence is higher in developing countries.[93] Therefore, well trained dentistry staff can serve as sentinels in the detection and early diagnosis of AIDS.[92 93] As key members of the treatment team, pharmacists often jointly develop treatment plans with doctors and counsel infected patients on drugs, to improve adherence to treatment.[94] The appropriate use of drugs for HIV pre-exposure prophylaxis and postexposure prophylaxes is also key to reducing infection and mortality rates.[95 96] Apart from the previously mentioned factors associated with HIV diagnosis and treatment, many social problems, policies, laws, ethics, and other factors about the HIV/AIDS epidemic affect health outcomes and are more likely to produce abnormal results of primary analysis. Under the premise of ensuring a strong development of HRH, we suggest that countries should widely promote social mobilization, especially in high prevalence and high mortality areas, and that effective measures should be broadly rolled out (see supplementary materials section 3.3.2 for literature review).

In addition, we also discovered the association between 16 HRH cadres and 20 other types of cause specific mortality, suggesting the importance of some HRH categories may have been underappreciated in the past. For instance, periodontitis seems to be associated with an increased risk of diabetes, due to infection or inflammatory responses, or both, whereas the periodontal treatment delivered by dentistry may lead to an improvement in glycemic control in people with type 2 diabetes.[97 98] Mental health comorbidities of diabetes can affect adherence to treatment, thereby increasing the risk of serious complications, which may then lead to premature death.[99] Optometrists are often the first to notice symptoms or signs of diabetes and other kidney disease by looking for changes in blood vessels in the eye, and thereby helping to improve diabetes outcomes.[100-102] Overall, the density of dentistry staff, psychologists, and optometrists warrants more attention in relation to deaths from diabetes and kidney diseases (see supplementary materials section 3.3 for other associations).

Time to strengthen the development of HRH

The governments of some countries affected by famine, ware, and pollution lack resources to deal with the shortage of HRH.[103-106] The covid-19 pandemic imposes additional burdens, particularly on HRH and deaths.[57] The growing scarcity of HRH in low to middle income countries makes it challenging to put HRH development on hold. The High-Level Commission on Health Employment and Economic Growth highlights that targeted investments in HRH contribute to economic growth.[107] The Brazilian government promoted the expansion of numbers of primary care doctors, and established new medical schools in 2013,[108] and the modest reduction in mortality was associated with the introduction of the programme.[108] Countries may need to share responsibilities (shared financing models); actively develop sustainable and mutually beneficial partnerships; respond to the human resource crisis through decentralization, central management coordination, and stakeholder participation in policy decision coordination processes; and expand fiscal space to fund health sector positions while investing in health worker education.[109 110]

Strengths and limitations of this study

Our findings highlight the importance of expanding the financing of health and developing equity oriented policies for the health workforce to reduce deaths related to an inadequate HRH. The demands for HRH vary from country to country because of the inherent inequities and constant changes in disease spectrums.[111] However, our study has several potential limitations. First, the quality and quantity of Global Burden of disease data chiefly depended on the validity and reliability of predictive models when data for certain years or locations were not available.[112] Therefore, when specific data were applied to countries and territories with underdeveloped medical systems, the findings needed to be interpreted with caution.[81] Second, some environmental data were utilized in the Global Burden of Disease estimation of mortality, but the means to measure these factors in low to middle income countries was limited. The lack of such data could lead to some underestimation of mortality in low to middle income countries.[113] Third, considering that most of the 32 excluded countries were at low development level, our findings might have underestimated the association between HRH density and mortality since we discovered a greater mortality effect in those countries ranked lower on the human development index. Nevertheless, our study has important implications for highlighting the positive health effects of HRH. We suggest that more countries and territories should establish high quality databases such as vital registration to help towards more comprehensive and rigorous research.

Conclusions

Although inequalities in HRH have been decreasing globally over the past 30 years but persist. All cause mortality and most types of cause specific mortality were relatively higher in countries and territories with a limited health workforce, especially for several specific HRH cadres among priority diseases, such as HIV/AIDS and sexually transmitted infections, maternal and neonatal disorders, diabetes and kidney diseases. Our findings reinforce the importance of political commitment being strengthened to develop equity oriented policies for health workforces by expanding the financing of health and implementing targeted interventions to reduce deaths as a result of inadequate HRH to achieve the timely goal of universal health coverage by 2030.

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Contributors: WXY and CYQ contributed equally and are joint first authors. WXY, CYQ, and JL conceptualized the study and performed the methodology and analysis. WXY and CYQ produced the original figures. CYQ and WXY drafted the manuscript. LYT, MD, QL, XG, LZ, ZDC, ML, and WNL contributed to critical revision of the manuscript. JL provided administrative, technical, and material support, and supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors approved the final version of the manuscript. JL is the study guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted

Funding: This study was funded by the National Natural Science Foundation of China (72122001, 72211540398, 71934002), National Statistical Science Research Project (2021LY038), National R and D Key project (2021ZD0114101, 2021ZD0114104, 2021ZD0114105), Beijing Natural Science Foundation of China (L222027), and National Science and Technology Project on Development Assistance for Technology, Developing China-ASEAN Public Health Research and Development Collaborating Center (KY202101004). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the paper. No payment was received by any of the coauthors for the preparation of this article.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the National Nature Science Foundation of China, National R and D Key project, and National Science and Technology Project on Development Assistance for Technology, Developing China-ASEAN Public Health Research and Development Collaborating Center for the submitted work; no financial relationships with any

organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required as this study used secondary data aggregated at both country and global level.

Data sharing: All data in the study are available at https://ghdx.healthdata.org/gbd-2019, http://data.un.org/, https://ourworldindata.org/. The analytic codes of this study are available on GitHub at https://github.com/cheng01zi/codes-for-inequalities-in-HRH.git.

The lead author (JL) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Dissemination of the results to all cadres of human resources of health, experts in the specialty of healthcare, and policy makers will be undertaken through the Global Scientific Data Platform for Prevention, Control and Management of Major Infectious Diseases at https://www.globalbigmid.com. Researchers involved in the study will disseminate the results to related officials and the public through professional bodies' websites and conferences at the national level.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: Additional methods, results, discussion, figures, and tables

frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 16 May 2023
DOI 10.3389/fcvm.2023.1212269

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 26 April 2023
ACCEPTED 02 May 2023
PUBLISHED 16 May 2023

CITATION
Gao D, Cai YS, Pan Y, Ma Q and Xie W (2023) Editorial: Epidemiology and clinical researches in atherosclerosis and cardiovascular disease. Front. Cardiovasc. Med. 10:1212269. doi: 10.3389/fcvm.2023.1212269

Editorial: Epidemiology and clinical researches in atherosclerosis and cardiovascular disease

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KEYWORDS

atherosclerosis, cardiovascular disease, epimiology, cohort study, dementia

Editorial on the Research Topic
Epidemiology and clinical researches in atherosclerosis and cardiovascular disease

Atherosclerosis is a systemic disease and the common cause of heart attacks, strokes and peripheral vascular disease collectively referred to as cardiovascular diseases (CVD), which are the leading cause of global mortality and a major contributor to disability and rising health care costs. Additionally, a wealth of epidemiological data demonstrated that atherosclerosis risk factors, including (but not limited to) hypertension, diabetes, and hyperlipidemia are associated with other chronic diseases such as chronic kidney disease, cognitive decline and dementia (1–6). The huge and still growing burden of CVD and dementia on individuals, families, and health-care systems indicates an urgent need for prevention and treatment measures on atherosclerotic diseases. Preventing severe atherosclerosis progression is expected to decrease high cardiovascular and dementia event rate.

However, there still exist challenges to be addressed. These challenges include but are not limited to (1) early detect participants with high-risk of CVD; (2) identify novel indicators for progression and prognosis of atherosclerotic diseases; (3) comorbidities of atherosclerotic diseases; (4) new drugs and therapies on atherosclerosis and CVD.

This research topic aimed at creating a forum for high-quality epidemiology and clinical researches in the field of atherosclerosis and CVD. The issue currently includes 12 papers on guiding comprehensive care and practice in preventing and managing major atherosclerotic CVD, including coronary heart disease, stroke, and peripheral vascular disease, and other chronic diseases which are associated with atherosclerosis.

In this topic, Wang et al. conducted a cohort study to explore the association between non-HDL-C and arterial stiffness on a large-scale Chinese population (https://www.frontiersin.org/articles/10.3389/fcvm.2022.981028/full). The results highlighted non-HDL-C as a potential risk factor for arterial stiffness, in especially for younger people. The clinical benefits of lowering non-HDL-C concentration should be further considered in the future.

Gao et al. performed a systematic review and meta-regression analysis to investigate the impact of statins on CRP/hsCRP reduction on coronary plaque burden measured using total atheroma volume (TAV), percent atheroma volume (PAV), and plaque volume (PV) (https://www.frontiersin.org/articles/10.3389/fcvm.2022.989527/full). After adjusting for percent change of LDL-C, age, gender and study duration, this meta-regression analysis mainly found that the percent change of CRP/hsCRP was significantly associated with the change of TAV/PV. The results indicated that statins promote plaque regression, which may be associated to their capacity to reduce inflammation.

In a multi-ethnic longitudinal cohort study, Anbar et al. compared carotid atherosclerosis in Europeans (EA), South Asian (SA), and African Caribbean (AC) participants in the Southall and Brent Revisited (SABRE) study and they found that the prevalence of any plaque was comparable in EA and SA, although it was lower in AC. Total plaque area, numbers of plaques, plaque class, or greyscale median did not differ by ethnicity in individuals who had plaque (https://www.frontiersin.org/articles/10.3389/fcvm.2022.1002820/full). This study indicated that the similarity of plaque burden in SA and EA despite established differences in atherosclerotic CVD risk casts some doubt on the utility of carotid ultrasound as a means of assessing risk across these ethnic groups.

Sundquist et al. performed a population-based follow-up study to examine the role of mtDNA-CN in heart failure (HF) incidence and its role in the association between myocardial infarction (MI) and HF. In addition, this study also investigated the role of mtDNA-CN in overall and HF mortality (https://www.frontiersin.org/articles/10.3389/fcvm.2022.1012403/full). This study mainly found that low baseline mtDNA-CN is a molecular risk factor for HF incidence and may be a risk factor for overall and HF-related mortality.

In a cohort study published in this topic (https://www.frontiersin.org/articles/10.3389/fcvm.2022.1026597/full), Moon et al. examined the association between height loss and the prevalence of CVD using data from a sizable Korean cohort. The participants were divided into three groups based on their annual height loss: Group 1 (height loss: <0.3 cm/year), Group 2 (height loss: 0.3 to <0.6 cm/year), or Group 3 (height loss: ≥0.6 cm/year). The results indicated that the incidence of major adverse cardiac and cerebral event was substantially higher in Groups 2 and 3 than in Group 1. In the Korean population, the severity of height reduction was independently correlated with the occurrence of CVD.

Muhammad et al. conducted a longitudinal two-cohort analysis, and identified association between positive triglyceride-glucose (TyG) index and increased arterial stiffness and increased incidence of diabetes, CE, stroke, and all-cause and cardiovascular mortality (https://www.frontiersin.org/articles/10.3389/fcvm.2022.1035105/full). The results of this work represent preliminary evidence that TyG index can potentially be helpful in the identification of those at increased long-term risk of adverse health outcomes.

A classification tree analysis (CTA) model established by Ruan et al. in this topic identified four key correlates of depressive disorders: loneliness was the most salient, followed by arthritis, family relationship, and heart disease (https://www.frontiersin.org/articles/10.3389/fcvm.2022.1035203/full). Due to the potential for modification or treatment, these findings regarding the four main correlates of depressive disorders are clinically interesting. The clinical needs for collaborative multidisciplinary management services—which integrate social work outreach services to foster family relationships, mental health services to relive loneliness, and primary care services to manage arthritis and heart disease—are further indicated by the significant interactions between the four major factors.

In a cohort study, Ma et al. recruited 299 patients with new-onset non-valvular atrial fibrillation (AF) between 2013 and 2015 at the Department of Cardiovascular Medicine of the Southwest Hospital of the Army Medical University (Third Military Medical University) in Chongqing, China (https://www.frontiersin.org/articles/10.3389/fcvm.2022.1072164/full). The findings revealed that throughout the median follow-up period of 28 (IQR: 27, 29) months, IL-34 and IL-38 were independently associated with stroke and all-cause mortality in patients with AF. Additionally, IL-38 and NT-proBNP considerably increased the CHA2DS2-VASc score's capacity to predict AF-related all-cause death.

In another large-scale cohort study, Hua et al. found that participants with and without heart disease experienced similar changes in global cognitive scores during the pre-pandemic period, however, in comparison to the group without heart disease, the heart disease group experienced a greater decline in the global cognitive score during the pandemic period (https://www.frontiersin.org/articles/10.3389/fcvm.2022.1077800/full). The findings highlight the need for rapid cognitive monitoring and therapies for the population suffering from heart diseases.

Grabitz et al. focused on exploring the early indicators and rivers of cardiovascular disease in young athletes pursuing a career in competitive sports (https://www.frontiersin.org/articles/10.3389/fcvm.2023.1081675/abstract). They discovered an unexpectedly high rate of cardiovascular risk factors despite regular exercise and the absence of obesity. Their findings suggested that children and young adults, who initially appeared to be in good condition, require rigorous medical examinations. To further investigate potential negative impacts on vascular health, long-term monitoring of those who began engaging in excessive physical activity as children and young seems required.

In this topic, Ni et al. employed linkage disequilibrium score (LDSC) regression and a two-sample Mendelian randomization (MR) framework to systematically examine the causal interplay between key factors that influence vascular calcification and CVD, as well as longevity (https://www.frontiersin.org/articles/10.3389/fcvm.2023.1096662/full). The results provide evidence for a causal relationship between VK1 levels and CVD risk as well as a genetic genetic correlation between serum Ca and VD

and CVD risk. Cardiovascular risk can be decreased by maintaining appropriate serum Ca (2.376 mmol/L) and VD levels (46.8 nmol/L).

In the last article published in this topic, Wright et al. examined associations between a history of pregnancy loss and incident CVD among participants in the Women's Health Initiative Observational Study (https://www.frontiersin.org/articles/10.3389/fcvm.2023.1108286/full). In this cohort study of postmenopausal women aged 50–79, history of stillbirth was strongly associated with a risk of cardiovascular outcomes within 5 years of baseline. Additionally, history of pregnancy loss, and of stillbirth, may be a therapeutically effective marker of cardiovascular disease risk in women.

In conclusion, the articles published in this research topic provide additional evidence from epidemiology and clinical researches for current literature on atherosclerosis and cardiovascular disease. Nevertheless, incredible challenges on the prevention and treatment of atherosclerosis and cardiovascular disease need more attention following the aging of the population and the development of social economy. We thank the authors for their cutting-edge works, and also express our gratitude to all the reviewers for their generously devoted time and highly valuable comments. Finally, we hope that the reader will enjoy these articles.

Author contributions

DG and WX drafted this manuscript, and all authors revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 2023, **XX**(XX), 1–8
https://doi.org/10.1093/gerona/glad128
Advance access publication 20 May 2023
Research Article

Identifying Potential Causal Effects of Telomere Length on Health Outcomes: A Phenome-Wide Investigation and Mendelian Randomization Study

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Decision Editor: Lewis A. Lipsitz, MD, FGSA

Abstract

Background: Telomere length has been linked to various health outcomes. To comprehensively investigate the causal effects of telomere length throughout the human disease spectrum, we conducted a phenome-wide Mendelian randomization study (MR-PheWAS) and a systematic review of MR studies.

Methods: We conducted a PheWAS to screen for associations between telomere length and 1 035 phenotypes in the UK Biobank (n = 408 354). The exposure of interest was the genetic risk score (GRS) of telomere length. Observed associations passing multiple testing corrections were assessed for causality by 2-sample MR analysis. A systematic review of MR studies on telomere length was performed to harmonize the published evidence and complement our findings.

Results: Of the 1 035 phenotypes tested, PheWAS identified 29 and 78 associations of telomere length GRS at a Bonferroni- and false discovery rate-corrected threshold; 24 and 66 distinct health outcomes were causal in the following principal MR analysis. The replication MR using data from the FinnGen study provided evidence of causal effects of genetically instrumented telomere length on 28 out of 66 outcomes, including decreased risks of 5 diseases in respiratory diseases, digestive diseases, and myocardial infarction, and increased risks of 23 diseases, mainly comprised neoplasms, diseases of the genitourinary system, and essential hypertension. A systematic review of 53 MR studies found evidence to support 16 out of the 66 outcomes.

Conclusions: This large-scale MR-PheWAS identified a wide range of health outcomes that were possibly affected by telomere length, and suggested that susceptibility to telomere length may vary across disease categories.

Keywords: Causality, Mendelian randomization, Phenome-wide association study, Telomere length

Telomeres, the DNA–protein complexes at the ends of eukaryotic chromosomes, are crucial for genomic stability and cell viability (1). Telomere length (most commonly measured as leucocyte telomere length) has been reported to be associated with a wide range of diseases, particularly common age-related diseases including cardiovascular diseases and cancer (2,3); however, the direction and magnitude of the associations are inconsistent across observational studies (4,5). Moreover, whether the links between telomere length and diseases are causal or confounded by lifestyle factors or comorbidities remains unclear.

Genome-wide association study (GWAS) identified genetic loci associated with telomere length (6), which can be used as instrumental variables in Mendelian randomization (MR) studies to determine evidence of causality (7). Nevertheless, current MR studies on telomere length are largely hypothesis-driven, focusing on a limited range of outcomes, resulting in a large proportion of disease associations that have yet to be more fully characterized. A hypothesis-free phenome-wide association study (PheWAS) combined with MR approach can comprehensively explore the causality across a spectrum of diseases without being limited to pre-existing disease associations (8). Such an analysis allows for a systematic appraisal of the health effects of telomere length and provides direction for further research.

In the present analysis, an MR-PheWAS was conducted using registry-based data from up to 408 354 participants from the UK Biobank to systematically investigate the causal

Received: March 3 2023; Editorial Decision Date: May 9 2023.

effects of telomere length on health outcomes. Besides, based on previous MR studies on telomere length, we also performed a systematic review to harmonize the evidence to complement the remaining possible outcomes.

Method

Study Design and Participants

We first performed a registry-based case–control PheWAS of telomere length and then assessed identified associations for causal inferences with the use of inverse-variance-weighted (IVW) MR accompanied by several other methods based on different assumptions. For a more comprehensive assessment, we further performed a systematic review of previous MR studies on telomere length. The schematic diagram of the study design is presented in Figure 1.

The phenome-wide MR analyses were undertaken in the UK Biobank, which comprised one-half million UK participants recruited between 2006 and 2010. Details of the study design have been described previously (9). The analyses in the present study were limited to White-British individuals with available genetic data following exclusion measures (sex mismatch, high missingness/heterozygosity, and excess relatives), leaving 408 354 participants in our analyses.

This research was conducted using the UK Biobank resource under application 44430. Ethics approval for the study was obtained from the National Information Governance Board for Health and Social Care and the North West Multicenter Research Ethics Committee (11/NW/0382). All participants provided written informed consent for the study.

Genetic Risk Score

A genome-wide meta-analysis identified 52 independent single nucleotide polymorphisms (SNPs) associated with leukocyte telomere length with a false discovery rate (FDR) adjusted p value of <.05 ($p < 1.03 \times 10^{-5}$), in 78 592 individuals of European ancestry (6) (Supplementary Table 1). Among them, 3 monoallelic SNPs were disregarded, and the instrumented SNPs explained 2.78% of the variance in leukocyte telomere length (R^2 = 2.78%, F-statistic = 1 983).

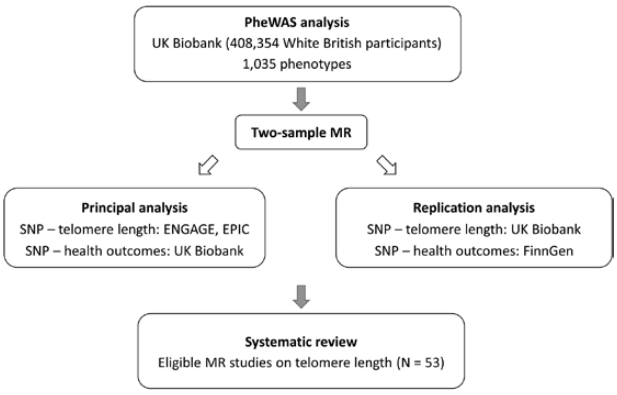

Figure 1. Schematic diagram of the study design. ENGAGE = European Network for Genetic and Genomic Epidemiology; EPIC = European Prospective Investigation into Cancer and Nutrition; GWAS = genome-wide association analysis; MR = Mendelian randomization; PheWAS = phenome-wide association study; SNP = single nucleotide polymorphism.

Genetic risk score (GRS) of telomere length was constructed by the weighted sums of individual risk alleles, where the weights were effect sizes from the GWAS (6). The weighted GRS was rescaled to reflect the number of telomere length-increasing alleles.

Statistical Analyses

In the first stage of the analysis, we performed the PheWAS to obtain evidence for the associations between the telomere length GRS and multiple health outcomes. Health outcomes were determined through inpatient hospital records (up to September 30, 2021), cancer (up to January 31, 2021), and death (up to October 31, 2021) registrations. International Classification of Diseases (ICD) versions 9 and 10 codes were extracted and converted into phenotype codes (phecodes) using a previously published schema (10), with both incident and prevalent cases included. We identified cases as individuals with at least one recorded event, and controls as individuals without that outcome recorded or its associated phecodes (10). Analysis was restricted to phecode with more than 200 cases to generate improved statistical power (11,12). A series of case–control groups were set up for each phecode, and a logistic regression was carried out for each phecode against the GRS, adjusting for age, sex, assessment center, and top 10 principal components. Multiple testing correction was based on Bonferroni- and FDR-corrected thresholds.

In the second stage of the analysis, we performed the 2-sample MR analysis for those observed associations with distinct outcomes passing multiple testing corrections in the PheWAS. The estimates of associations between SNP and telomere length were extracted from the GWAS (6), and the estimated associations of SNP and outcomes were determined using the UK Biobank. We removed SNPs that suggested greater variance in the outcomes than telomere length using Steiger filtering. Primary analyses were performed using IVW MR, yielding reliable causal estimates in the absence of horizontal pleiotropy (13). The association in the 2-sample MR with a $p < .05$ was considered as statistically significant. To assess the stability of estimation, we performed sensitivity analyses including MR-Egger, weighted median, and MR-PRESSO methods. MR-Egger regression relaxes the requirement of no horizontal pleiotropy among the SNPs; however, corresponding associations tend to suffer from low statistical power (14). A nonzero intercept from the MR-Egger regression indicates unbalanced horizontal pleiotropy (14). The weighted median method can produce consistent estimates when more than half of the information in the MR analysis comes from valid instruments (15). MR-PRESSO analysis includes a global test to detect horizontal pleiotropy, an outlier test to detect potentially pleiotropic outliers, and a distortion test of significant differences in the causal estimates before and after outlier removal (16). The outlier-adjusted causal estimates were presented for associations where both the global and distortion tests provided evidence of horizontal pleiotropy ($p < .05$). Statistical power for each outcome in 2-sample MR analyses was assessed based on an online tool (17).

To validate the findings, we further replicated our 2-sample MR results in external outcome summary statistics. Instrumental variables were 130 independent, uncorrelated, and nonpleiotropic genome-wide significant SNPs related to telomere length extracted from a GWAS involving 472 174 participants in UK Biobank (Supplementary Table 2) (18). Summary-level outcome data was based on FinnGen, which is

a research project involving around 26 900 participants that combines genotype data from Finnish biobanks and digital health record data from Finnish health registries. Detailed information on FinnGen has been shown previously (19).

The statistical analyses were conducted using Stata version 15 (StataCorp LLC, College Station, TX) and R packages titled phewas, TwoSampleMR, and MR-PRESSO in R software version 4.0.2 (R Foundation, Vienna, Austria).

Systematic Review of Previous MR Studies on Telomere Length

A systematic review of MR studies on telomere length was performed to complement our MR-PheWAS findings. We searched in the PubMed database using the query "('telomere'[Mesh] OR telomere[tiab]) AND ('Mendelian Randomization'[Mesh] OR mendelian[tiab])" on April 10, 2023. We extracted the following characteristics from each included study: the first author's name and year of publication; the number of instrumented SNPs, and the exposure unit; the number of cases and controls; and the association estimates for the primary analysis.

Results

PheWAS Analysis

Baseline characteristics of the study participants are presented in Table 1. Among 408 354 participants, the mean (standard deviation [*SD*]) age was 56.9 (8.0) years, and 220 765 (54.1%) were female. A total of 1 853 phenotypes were defined. After excluding outcomes with cases less than 200, the remaining 1 035 phenotypes were classified into 18 disease categories and their associations with telomere length GRS were examined (Supplementary Table 3). Of the 1 035 phenotypes tested, our PheWAS analysis identified 29 and 78 associations of telomere length GRS covering 7 and 13 disease categories at a Bonferroni- ($p < 4.2 \times 10^{-5}$; based on 0.05/1035) and FDR-corrected threshold ($p < 3.8 \times 10^{-3}$; based on 0.05 × 78/1 035), respectively. The distribution of the results across disease categories is shown in Figure 2, and Supplementary Table 4 describes the results and the direction of the effects in detail. The associations with the lowest *p* values were for uterine leiomyoma (odds ratio [OR] per telomere length-increasing allele 1.04, 95% confidence interval [CI] 1.03–1.04; $p = 5.8 \times 10^{-25}$), hyperplasia of prostate (OR 1.02, 95% CI 1.02–1.03; $p = 7.1 \times 10^{-19}$), postinflammatory pulmonary fibrosis (OR 0.95, 95% CI 0.93–0.96; $p = 5.7 \times 10^{-15}$), and celiac disease (OR 0.95, 95% CI 0.93–0.96; $p = 9.8 \times 10^{-15}$).

Table 1. Baseline Characteristics of Participants in the UK Biobank

Characteristics	All Participants
No.	408 354
Age, years	56.9 (8.0)
Male	187 589 (45.9)
T/S ratio	0.74 (0.12)
College or university degree	125 219 (30.7)
Townsend Deprivation Index	−1.6 (2.9)
Current smoker	41 245 (10.1)
Daily drinker	86 340 (21.1)
Household income >100 000£	18 158 (4.5)
Body mass index, kg/m^2	27.4 (4.8)
Systolic blood pressure, mmHg	138.3 (18.6)
Cholesterol, mmol/L	5.7 (1.1)
Antihypertensive medications	41 320 (10.1)
Lipid-lowering medications	71 338 (17.5)

Notes: Mean (*SD*) for continuous variables and number (percentage) for categorical variables. T/S ratio = the relative leucocyte telomere length adjusted for the effect of technical parameters. *SD* = standard deviation.

Two-Sample MR Analysis

The principal IVW MR method provided evidence of a causal effect of genetically instrumented telomere length on 24 and 66 distinct health outcomes that passed the initial PheWAS screening at the Bonferroni- and FDR-corrected threshold (Supplementary Table 5). Of the 66 outcomes, our study was powered to detect at least a 50% increase for 57 disease risks in each SD increase ($\alpha = 5\%$, power 80%, $r^2 = 2.78\%$; Supplementary Table 6). The lowest *p* values were observed for polyp of corpus uteri (OR per *SD* longer telomere length 1.66, 95% CI 1.42–1.95), uterine leiomyoma (OR 1.93, 95% CI 1.56–2.39), disorder of skin and subcutaneous tissue (OR 1.39, 95% CI 1.24–1.56), postinflammatory pulmonary fibrosis (OR 0.35, 95% CI 0.24–0.50), and essential hypertension (OR 1.20, 95% CI 1.12–1.28). We obtained similar associations with the weighted median and MR-PRESSO approaches, whereas the MR-Egger method tended to be more conservative and yielded less strong associations (Supplementary Table 5). MR-Egger pleiotropy test suggested the presence of directional pleiotropy for 7 associations, including melanomas of skin, secondary malignancy of bone, polycythemia vera, multiple myeloma, noninfectious disorders of lymphatic channels, diseases of hair and hair follicles, and acute and chronic tonsillitis, but the results still supported the MR IVW analysis in both direction and significance (Supplementary Table 5). The MR-PRESSO method identified outliers for cancer of brain and bronchus, celiac disease, and hyperplasia of prostate, but only the association of brain cancer was attenuated to insignificant after removal of outliers (Supplementary Table 5).

We used available outcome data from FinnGen to validate our principal 2-sample MR results (Supplementary Table 7). By use of IVW MR method, we replicated 28 significant disease outcomes that were identified in the principal MR analysis (Figure 3). Among these outcomes, longer telomere length was associated with an increased risk of 14 neoplasms, 6 diseases in the genitourinary system, and essential hypertension. Conversely, longer telomere length was associated with decreased risk of 2 diseases in the respiratory system, 2 diseases in the digestive system, and myocardial infarction.

Systematic Review for MR Studies on Telomere Length

An initial search revealed 184 potentially relevant articles, of which 77 remained after title and abstract screening. We further excluded 24 out of 77 studies after full-text screening. A flowchart showing the number of studies found in our search strategy, and reasons for exclusion are given in Supplementary Figure 1. Detailed information on the 53 eligible studies is shown in Supplementary Table 8. Among

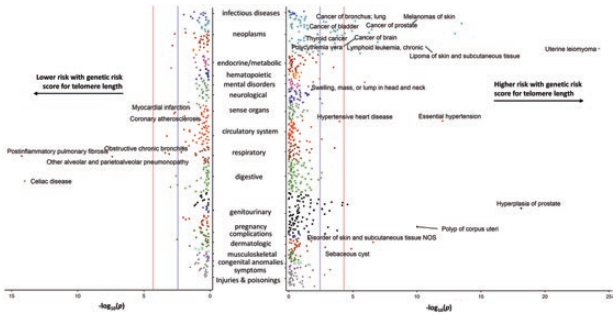

Figure 2. Manhattan plots illustrating the phenome-wide association between telomere length genetic risk score (GRS) and health outcomes. X-axes correspond to the minus log transformed *p* value derived from phenome-wide association analyses; Y-axes correspond to the list of labels of 18 disease categories. The red lines indicate the Bonferroni-corrected threshold ($p < 4.2 \times 10^{-5}$), and the blue lines indicate the FDR-corrected threshold ($p < 3.8 \times 10^{-3}$).

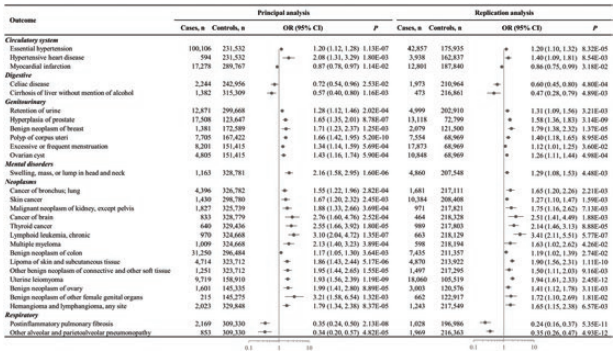

Figure 3. Inverse-variance weighted Mendelian randomization analyses on the associations of telomere length and health outcomes. CI = confidence interval; OR = odds ratio.

these studies, 16 of these reported distinct disease outcomes shared consistent results with our principal 2-sample MR, demonstrating that telomere length was associated with multiple cancers, hypertension, coronary heart disease, myocardial infarction, abdominal aortic aneurysm, interstitial lung disease, idiopathic pulmonary fibrosis, and celiac disease (Table 2). Furthermore, the systematic review found several additional outcomes, including increased risk of endometrial, breast and ovarian cancer, systemic lupus erythematosus, ankylosing spondylitis, and decreased risk of type 1 diabetes, rheumatoid arthritis, multiple sclerosis, chronic kidney disease, Alzheimer's disease, and bipolar disorder (Table 2). Although the majority of the associations were directionally consistent with our 2-sample MR, these associations were not statistically significant after multiple corrections in our analysis. The systematic review of MR studies also found causal associations with clonal hematopoiesis, amyotrophic lateral sclerosis, androgenetic alopecia, and periodontitis that were not captured sufficient data in phecodes.

Discussion

In performing the MR-PheWAS of telomere length, as well as additional evidence from systematic review, we obtained evidence of wide-ranging implications for telomere length on health, and our findings suggested that susceptibility to telomere length may vary across disease categories. Among these diseases, longer telomere length was associated with increased risk of neoplasms, diseases of the genitourinary system, and essential hypertension, and decreased risk of diseases of the respiratory system and digestive system, and myocardial infarction.

Several associations we found in the MR-PheWAS analysis were in line with previous MR findings, including the associations of longer telomere length with decreased risk of diseases of respiratory diseases (20,21), coronary artery diseases (22,23), celiac disease (20), and increased risk of multiple neoplasms (20,24–28) and hypertension (22). As a result, our findings further added to the causal evidence of these associations. A previous PheWAS in the UK Biobank found that measured longer telomere length was negatively related to diseases of respiratory, digestive, and circulatory (particularly arterial disease) systems, whereas positively associated with neoplasms, and this observational study, consistent with our genotype-based MR findings, is a substantial addition to our results (29). In addition, the aforementioned study found that telomere length-related SNPs were associated with the risk of postinflammatory pulmonary fibrosis and sickle cell anemia (29). However, the study used single SNPs as genetic instruments that explained less than 0.7% of the phenotypic variance of telomere length (30) and might therefore have overlooked weak-to-moderate associations due to inadequate power. Here, our multi-SNP approach increased statistical power and enabled us to use several complementary MR methods to validate our causal findings. We reported causal associations more broadly, including benign neoplasms such as uterine leiomyoma, benign neoplasm of skin, ovary, and colon and genitourinary diseases such as retention of urine, hyperplasia of prostate, polyp of corpus uteri, and ovarian cyst, and the earlier diseases have rarely been studied despite their high prevalence.

The systematic review of MR studies on telomere length found several associations we observed in the present MR-PheWAS analysis and expanded the causality that was not captured in phecodes. Although our MR results showed directionally consistent associations with those previously reported diseases that extended to diseases of musculoskeletal (31), neurological (32), dermatologic (33), endocrine systems (20), and mental disorders (34), these associations were not statistically significant after multiple corrections in the present PheWAS, which may be the result of insufficient statistical power, especially for those outcomes with fewer cases. In addition, current causal evidence on telomere length has been limited to European populations. Future large-scale trans-ethnic meta-analyses will be crucial in determining shared telomere length causal associations.

Several mechanisms might explain identified associations. The underlying mechanisms by which long telomere length increase multiple cancer risk could be explained by telomere shortening may serve as a tumor suppressor potentially through limiting the cell proliferative capacity, and individuals with shorter telomeres are more likely to reduce the acquisition of potential oncogenic mutations during DNA replication (6,35). One hypothesis for the association between telomere shortening and increased risk of genitourinary diseases may be that genitourinary disorders are precursor lesions and could be a marker in the development of genitourinary tumors (36). Notably, the inverse associations observed in some other non-neoplastic diseases may reflect

Table 2. Comparison of the Results from the Systematic Review of MR Studies and the Present MR-PheWAS

Year	First Author	SNPs	Outcome*	Cases	OR (95% CI)†	Results in the Present MR-PheWAS	
						Corresponding Phecode	OR (95% CI)
Neoplasms							
2017	Philip Haycock	16	Glioma	1 130	5.27 (3.15–8.81)	191.11	2.76 (1.60, 4.76)
2022	Charlie N Saunders	16	Glioma	12 488	4.79 (2.11–10.85)	191.11	2.76 (1.60, 4.76)
2020	A E Howell	15	Glioma	5 739	4.09 (1.13–14.86)	191.11	2.76 (1.60, 4.76)
2019	Ivo S. Muskens	8	Meningioma	1 053	1.06 (1.03–1.10)	225.1	1.88 (1.23, 2.87)‡
2022	Lulu Huang	16	Thyroid cancer	989	4.68 (2.35–9.31)	193	2.55 (1.66, 3.92)
2015	Chenan Zhang	9	Lung cancer	12 160	1.65 (1.39–1.96)	165.1	1.55 (1.22, 1.96)
2017	Philip Haycock	16	Lung cancer	3 442	3.19 (2.40–4.22)	165.1	1.55 (1.22, 1.96)
2019	Linda Kachuri	8	Lung cancer	16 396	1.39 (1.21–1.60)	165.1	1.55 (1.22, 1.96)
2019	Xuguang Cao	9	Lung cancer	7 127	2.25 (1.81–2.78)	165.1	1.55 (1.22, 1.96)
2022	Nannan Son	17	Melanoma	3 751	1.01 (1.00-1.02)	172.11	1.71 (1.36, 2.15)
2018	Sivaramakrishna Rachakonda	3	Melanoma	1 469	2.66 (2.07–3.25)	172.11	1.71 (1.36, 2.15)
2017	Philip Haycock	16	Skin cancer	12 814	1.87 (1.55–2.26)	172	1.67 (1.20, 2.32)
2020	Yifan Xu	11	Soft tissue sarcoma	821	1.44 (1.18–1.75)	170.2	2.23 (1.41, 3.53)
2019	Chia-Ling Kuo	13	Breast cancer	12 382	1.06 (1.01–1.12)	174	1.08 (0.80, 1.46)‡
2022	Fa Chen	19	Breast cancer	133 384	1.19 (1.08–1.32)	174	1.08 (0.80, 1.46)‡
2020	Molly Went	7	Multiple myeloma	7 717	2.33 (1.20–4.52)	204.4	2.13 (1.40, 3.23)
2019	Daniele Campa	10	Pancreatic cancer	2 374	0.88 (0.85–0.92)	157	0.95 (0.66, 1.38)‡
2017	Philip Haycock	16	Bladder cancer	1 601	2.19 (1.32–3.66)	189.2	1.61 (1.20, 2.17)
2017	Philip Haycock	16	Kidney cancer	2 461	1.55 (1.08–2.23)	189.11	1.88 (1.33, 2.66)
2017	Mitchell J Machiela	9	Renal cell carcinoma	10 784	2.07 (1.70–2.53)	189.11	1.88 (1.33, 2.66)
2017	Philip Haycock	16	Endometrial cancer	6 608	1.31 (1.07–1.61)	182	1.40 (1.10, 1.78)‡
2017	Philip Haycock	16	Ovarian cancer	972	4.35 (2.39–7.94)	184.11	1.42 (1.04, 1.92)‡
2023	Wenjie Li	125	Basal cell carcinoma	17 416	1.53 (1.35–1.74)	172.21	-
Circulatory system							
2019	Chia-Ling Kuo	13	Hypertension	120 790	1.06 (1.03–1.09)	401.1	1.20 (1.12, 1.28)
2022	Yingjian Deng	130	Hypertension	55 917	1.12 (1.02–1.23)	401.1	1.20 (1.12, 1.28)
2022	Yingjian Deng	128	Myocardial infarction	11 622	0.72 (0.63–0.83)	411.2	0.87 (0.78, 0.97)
2017	Yiqiang Zhan	7	Coronary heart disease	22 233	0.79 (0.65–0.97)	411.4	0.89 (0.81, 0.98)
2019	Chia-Ling Kuo	13	Coronary heart disease	31 689	0.95 (0.92–0.98)	411.4	0.89 (0.81, 0.98)
2017	Philip Haycock	16	Coronary heart disease	22 233	0.78 (0.67–0.90)	411.4	0.89 (0.81, 0.98)
2017	Philip Haycock	16	Abdominal aortic aneurysm	4 972	0.63 (0.49–0.81)	442.11	0.65 (0.48, 0.86)
2022	Junkui Wang	118	Calcific aortic valvular stenosis	9 153	0.76 (0.63–0.92)	—	—
Neurological system							
2022	Qiao Liao	20	Multiple sclerosis	47 429	0.50 (0.38–0.66)	335	1.18 (0.80, 1.74)‡
2021	Kailin Xia	10	Amyotrophic lateral sclerosis	20 806	0.85 (0.74–0.96)	334.21	—
Respiratory system							
2017	Philip Haycock	16	Interstitial lung disease	1 616	0.09 (0.05–0.15)	504	0.34 (0.20, 0.57)

Table 2. Continued

Year	First Author	SNPs	Outcome*	Cases	OR (95% CI)†	Results in the Present MR-PheWAS	
						Corresponding Phecode	OR (95% CI)
2021	Anna Duckworth	7	Idiopathic pulmonary fibrosis	4 037	0.17 (0.11–0.28)	502	0.35 (0.24, 0.50)
Dermatologic system							
2022	Xu-Fan Wang	7	Systemic lupus erythematosus	5 201	2.96 (1.58–5.55)	695.42	1.09 (0.56, 2.11)‡
2023	Yicheng Li	126	Androgenetic alopecia	98	0.24 (0.07–0.83)	—	—
Digestive system							
2017	Philip Haycock	16	Celiac disease	4 533	0.42 (0.28–0.61)	557.1	0.72 (0.54, 0.96)
2022	Jiaxin Hu	133	Periodontitis	18 979	0.94 (0.91–0.98)	523.3	—
Endocrine system							
2017	Philip Haycock	16	Type 1 diabetes	7 514	0.71 (0.51–0.98)	250.1	1.06 (0.84, 1.33)‡
2022	Meijie Ye	9	Graves' disease	2 176	0.61 (0.46–0.81)	242.1	0.65 (0.42, 1.00)‡
Genitourinary system							
2021	Sehoon Park	52	Chronic kidney disease	41 395	0.83 (0.75–0.93)	585.3	1.05 (0.92, 1.19)‡
Hematopoietic system							
2022	Siddhartha P. Kar	116	Clonal hematopoiesis	10 203	1.56 (1.25-1.93)	—	—
2022	Tetsushi Nakao	16	Clonal hematopoiesis	5 490	2.46 (1.93-3.00)	—	—
Musculoskeletal system							
2020	Zhen Zeng	7	Rheumatoid arthritis	911	0.68 (0.54-0.86)	714.1	0.94 (0.72, 1.23)‡
2023	Donglei Wei	92	Ankylosing spondylitis	2 252	1.55 (1.14-2.11)	715.2	1.63 (0.94, 2.85)‡
Mental disorders							
2017	Philip Haycock	16	Alzheimer's disease	17 008	0.84 (0.71–0.98)	290.11	0.99 (0.77, 1.29)‡
2020	Alexander Madrid	4	Alzheimer's disease	25 580	0.93 (0.86–0.99)	290.11	0.99 (0.77, 1.29)‡
2021	Guangping Yu	17	Alzheimer's disease	35 274	0.79 (0.67–0.93)	290.11	0.99 (0.77, 1.29)‡
2022	Blanca Rodríguez-Fernández	21	Alzheimer's disease	71 880	0.96 (0.94–0.99)	290.11	0.99 (0.77, 1.29)‡
2023	Likui Lu	133	Bipolar disorder	7 647	0.80 (0.65–0.99)	296.1	0.86 (0.62, 1.19)‡

Notes: CI = confidence interval; MR = Mendelian randomization; OR = odds ratio; PheWAS = phenome-wide association study; SNP = single nucleotide polymorphism.
*Presented disease outcomes are those for which significant results were obtained in the systematic review.
†The OR (95% CI) reported here refers to the MR results in the systematic review, unified into the effect of per unit increase in the telomere length on the outcomes.
‡The OR (95% CI) are nonstatistically significant results reported by the present MR-PheWAS after multiple corrections.

the evolutionary trade-off between greater resistance to cancer at the cost of greater susceptibility to degenerative diseases (37). For respiratory diseases, short telomere length is also reported to be associated with lower arterial PO_2 and there are indications that telomere shortening lowers the threshold for chronic cigarette smoke-induced damage (38,39). We found that longer telomere length was related to an increased risk of essential hypertension, contrary to findings regarding degenerative diseases such as coronary atherosclerosis and myocardial infarction. However, the biological mechanism between telomere length and hypertension is less understood and may reflect the dynamic relationship between telomere maintenance and function during vascular aging (40). Future research into the specific mechanisms of how telomere length causes multiple diseases is warranted, which can help define a critical role of telomere length and bring greater attention to telomere-related prevention, diagnosis, and treatment.

One of the strengths of our study was that the MR-PheWAS analysis was performed, allowing for evidence of causal associations between telomere length and a wide range of diseases, which is less susceptible to residual confounding and reverse causality than traditional observational studies. Another major novelty of the present study is to perform a systematic review of MR studies on telomere length to complement findings not captured in our results. In addition, other strengths included a large sample size, the availability of thorough information on hospital admissions and death registrations, and the conduct of several complementary methods to ensure the robustness of

results. However, the present study has several potential limitations. First, the majority of cases were identified from hospital records in the PheWAS analysis, which may affect the coverage of case ascertainment, particularly for diseases that do not typically require hospitalization; although we have included 1 035 phenotypes with case counts greater than 200, it is still possible that for diseases with relatively low prevalence, no significant association could be found because of low efficacy. Second, population stratification may introduce bias. To minimize this possibility, we limited our study to individuals of White-British ancestry and adjusted for assessment center and genetic principal components that account for population structures. However, we acknowledged that the extrapolation of our findings to other races and ethnicities may be limited. Third, some of the observed correlations suggested the presence of directional pleiotropy. Thus, caution is needed in the interpretation of such associations in particular due to known pleiotropic effects. Fourth, our genetic instrumental variables were derived from the GWAS in the adult population, which reflects the cumulative effect of genes over the life course on adult telomere length. Therefore, estimates derived using our GRS may not fully reflect the impact of telomere length on disease risk across all life stages. Finally, leukocyte telomere length was chosen for analysis as a surrogate and may not directly reflect the telomere length in other tissues.

In summary, our phenome-wide MR and systematic review provided evidence of wide-ranging implications for telomere length on health outcomes. Our findings indicated the potential protective effect of longer telomere length on respiratory diseases, digestive diseases, and myocardial infarction, and the detrimental effect on neoplasms, diseases of the genitourinary system, and essential hypertension. Overall, our findings expand current knowledge on the effects of telomere length on human diseases and suggested that susceptibility to telomere length may vary across disease categories. Further research are warranted to determine whether telomere length is a useful risk predictor for guiding preventive and therapeutic interventions and to explore modifiable mechanisms to alleviate the detrimental effect of telomere length.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

The study was supported by grants from the National Key Research and Development Program of China (2020YFC2003401).

Conflict of Interest

None declared.

Acknowledgments

We are grateful to all the participants of the UK Biobank and all the people involved in building the large biobank. This research was conducted using the UK Biobank resource under application 44430.

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International Journal of Stroke
WSO

International Journal of Stroke
1–9

DOI: 10.1177/17474930231172623
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Is statin therapy after ischaemic stroke associated with increased intracerebral hemorrhage? The association may be dependent on intensity of statin therapy

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Abstract

Background: There has been concern that statin therapy may be associated with an increased risk of intracerebral hemorrhage (ICH). We investigated whether the intensity and type of statin therapy instituted after ischemic stroke (IS) were associated with risk of future ICH in a region of northern China with a high incidence of stroke.

Methods: Newly diagnosed IS patients who were not treated with lipid-lowering drugs in the Beijing Employee Medical Claims Data database from 2010 to 2017 were included. The primary exposure variable was any statin prescription within 1 month of the first documented stroke diagnosis. High-intensity statin therapy was defined as atorvastatin ⩾ 80 mg, simvastatin ⩾ 80 mg, pravastatin ⩾ 40 mg, and rosuvastatin ⩾ 20 mg per day or equivalent combination. An adjusted Cox proportional hazards model was used to estimate the hazard ratio (HR) for ICH during follow-up in groups exposed and not exposed to statins.

Results: Of 62,252 participants with IS and 628 ICH readmissions were recorded during a median follow-up of 3.17 years. The risk of ICH among statin users (N = 43,434) was similar to that among nonusers (N = 18,818) with an adjusted HR and 95% confidence interval (CI) of 0.86 (0.73, 1.02). Compared with non-statin therapy, patients with low/moderate-intensity therapy had a lower risk of ICH (0.62: 0.52, 0.75), while patients with high-intensity therapy had a substantially higher risk (2.12: 1.72, 2.62). For patients with different types of statin therapy, adherence to rosuvastatin had the lowest risk of ICH compared to adherence to atorvastatin (0.46: 0.34, 0.63), followed by simvastatin (0.60: 0.45, 0.81).

Conclusion: In patients with IS, any statin therapy was not associated with an increased risk of ICH. However there appeared to be differential risk according to the dose of statin with high-intensity statin therapy being associated with an increased risk of ICH, while low/moderate-intensity therapy was associated with a lower risk.

Keywords
Stroke, cholesterol, Beijing, cohort study

Received: 3 February 2023; accepted: 1 April 2023

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Introduction

Statins have been widely reported to be effective cholesterol-lowering drugs, reducing mortality and the risk of cardiovascular events.[1,2] Although many cardiovascular benefits of statins have been recognized, concerns have been raised that statin therapy might be associated with an increased risk of intracerebral hemorrhage (ICH), particularly for those with cerebrovascular events.[3–5]

Evidence from existing studies is inconsistent, with statin use in patients with ischemic stroke (IS) reported to be unrelated to[6,7] or protective against ICH.[8] However, the potential risk of ICH with high-intensity statin therapy was documented.[5,9] Until now, high-intensity statin therapy has been advocated for post-stroke treatment, but the effect of statin intensity on ICH after IS remains controversial. Several studies suggest that the higher risk of ICH with high-dose statin therapy should be noted, especially in patients with IS after thrombolytic therapy,[3,9] while others do not yet support such a dose–response association.[6] In addition, different statins differ in terms of clinical efficacy and side effects.[5,10] Rosuvastatin has been reported to be superior to atorvastatin in the prevention of cardiovascular events, suggesting that rosuvastatin may be superior to atorvastatin in patients at high cardiovascular risk.[11–13] However, to date, evidence to support tailoring the type or dose of statins for safety concerns of ICH is limited, especially in the treatment of patients with IS.[14]

Globally, East Asia had the highest incidence rate of IS and the most pronounced increase, especially in China,[15] resulting in a huge population of disability and a serious economic burden.[16] However, evidence from large-scale population studies on the association of post-IS statin therapy with ICH is lacking. Therefore, this study aims to assess the relationship between the use, intensity, and type of statins and ICH readmission in patients with newly diagnosed IS in Beijing, a megacity in China, from 2010 to 2017.

Methods

Data source

Details of the Beijing Medical Claim Data for Employees (BMCDE) database have been previously described elsewhere.[17,18] Briefly, anonymous medical claim data, such as demographic characteristics, clinical diagnosis, medication and reimbursement information, of all active or retired employees enrolled in basic medical insurance in Beijing (nearly 90% of Beijing's permanent population) were registered into the database. Because the data we used were retrospective information encrypted for administrative purposes, our research was exempt from ethics committee review.

Study population

We included patients ⩾18 years of age with newly diagnosed IS and documented hospitalization who were enrolled in Medicare between 2010 and 2017. Clinical diagnostic information was presented in the International Classification of Disease edition 10 (ICD-10) code, as well as descriptive texts. IS was identified by ICD-10 coding (I63) or text diagnosis. "Newly diagnosed" was defined by applying a fixed 24-month look-back period in which the patient had continuous data coverage but did not have any records of IS. The earliest registry hospitalization of IS was used as the index hospitalization for patients with multiple registry hospitalizations. To explore the effect of post-stroke statin therapy, eligible patients had no records of statins or other cholesterol-lowering drugs (fenofibrate, niacin, probucol, etc.) in the 12 months prior to the first diagnosis of IS. Subjects were excluded if they (1) had a previous history of primary diagnosis of hepatic failure (ICD-10: K70-K72 or text diagnosis, N = 20) or severe kidney disease (ICD-10: I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61 and text diagnosis, N = 804) and (2) died within a month (N = 1491).

Statin exposure

Drug information includes brand and generic drug names, formulations, costs, and dispensing dates. The primary exposure variable was any statin prescription within 1 month of the first documented stroke diagnosis. Among patients who received any statin therapy, secondary exposure variables were high versus low/moderate intensity of statin use and types of statin adherence. High-intensity statin therapy was defined as atorvastatin ⩾ 80 mg, simvastatin ⩾ 80 mg, pravastatin ⩾ 40 mg, and rosuvastatin ⩾ 20 mg per day or equivalent combination.[3,19] Low/moderate-intensity statin therapy was defined as all other statin agents. Types of statin adherence were indicated by the proportion of days covered (PDC) ⩾ 80% for each type of statin during follow-up[20,21] (PDC = days covered by the prescription/days between the first prescription fill date and the end date).[22] Patients who adhered to two or more types of statins were not considered in the analysis of the effects of different types of statins.

Ascertainment of outcome

ICH readmission was defined as receiving any records of ICD-10 code diagnosis (I60-I62) or text diagnosis after IS. Information on deaths was obtained from the Medicare Death Registry. Patients were followed from the date of IS diagnosis (baseline) until the earliest ICH event occurred, death, withdrawal from the database, or termination on 31 December 2017, whichever occurred first.

Covariates

Sociodemographic factors (sex and age), medical resource utilization, comorbidities, and stroke-related concomitant prescription medication at baseline were assessed at the index day. Medical resource utilization includes designated hospital level for medical insurance and the number of outpatient and hospital visits in the 12 months prior to baseline. Comorbidities were identified from inpatient and outpatient records from 1 January 2008 to baseline by ICD-10 coding and text diagnosis. We established Charlson comorbidity indexes for patients based on their multisystem comorbidities to reflect the baseline health status, as detailed in the construction method described in a previous study.[23] In addition, baseline records of concomitant prescription drugs, including antihypertensive, anticoagulant (heparin, warfarin, rivaroxaban, and other thrombin inhibitors), antiplatelet (aspirin, clopidogrel, etc.), nonsteroidal anti-inflammatory drugs (NSAIDs), and thrombolytic drugs (Alteplase, streptokinase, urokinase, etc.), were also included in the analysis.

Statistical analysis

The respective distributions of baseline characteristics compared among patients receiving any versus no statin and high, low/moderate-intensity statin versus no statin were shown as frequencies with percentages for categorical variables and means with standard deviations for continuous variables. Variance between groups was evaluated with χ^2 tests for categorical variables and Kruskal–Wallis tests for continuous variables.

Unadjusted Kaplan–Meier incidence curves and log-rank tests were used to evaluate the ICH incidence in different intensity groups and types of statin adherence groups after the index date (high, low/moderate intensity versus none and rosuvastatin, simvastatin versus atorvastatin). Cox regression models were used to estimate the adjusted hazard ratios (HRs) for the risk of ICH in statin users compared with nonusers (high, low/moderate-intensity statin compared with no statin, rosuvastatin, simvastatin compared with atorvastatin adherence), adjusting for gender, age, comorbidities, hospital level, medical resource utilization, and concomitant medication prescription. In addition, adjusted HRs and 95% confidence intervals (CIs) were calculated for different statin treatment patterns (different intensities and types), stratified according to the time interval between baseline IS and ICH readmission. The proportionality hazard hypothesis was tested using Schoenfeld residuals and no proportionality bias was observed. The Fine-Gray model of competitive risk regression was used to further account for the competing risk of mortality, and the covariates were adjusted as above. Since differences in patient characteristics may affect the outcomes of statin therapy, a series of subgroup analyses were constructed, including age (<60 versus $\geqslant 60$ years), sex (male versus female), hospital rank (primary/secondary versus tertiary), comorbidity index (0–1 versus $\geqslant 2$), number of visits (0–2 versus >2), history of hypertension, use of anticoagulants, and thrombolytic therapy.

To account for the effect of any statin use throughout the follow-up period after IS and to make the basic characteristics of the treated and nontreated groups more consistent, we defined any statin use after stroke as the treatment group. To optimize the comparability of users and nonusers in terms of confounding factors, they were matched 1:1 within a caliper of 0.01 times the standard error of the logit propensity score for age, sex, first stroke date, type of stroke, hospital rank, medical resource utilization, comorbidities, and concomitant medication prescription. The standardized mean difference (SMD) of acceptable matching was less than 0.1. Other sensitivity analyses were conducted by (1) excluding participants with atrial fibrillation (AF), (2) excluding subarachnoid hemorrhage as an outcome that could be attributed to ruptured cerebral aneurysms or arteriovenous malformations rather than statin-mediated changes in serum cholesterol, (3) excluding patients who received thrombolytic therapy to rule out thrombolysis-related ICH, and (4) using a competing-risk regression model to further examine the competing risks of other cardiovascular diseases including various heart diseases and valvular diseases, hypertension, coronary heart disease, heart failure, and atherosclerosis (ICD-10: I01-I11, I13, I20-I51, I70).

A two-sided p value of <0.05 was considered to be statistically significant. All statistical analyses were performed by using Stata (version 14.0, StataCorp).

Results

Baseline characteristics

A total of 62,252 remaining patients with newly diagnosed IS were enrolled in this study, of whom 43,434 (69.8%) initiated statin treatment at baseline and 18,818 (30.2%) were nonusers (Table 1). Differences in the distribution of basic characteristics between the two groups were mainly indicated by younger age, fewer women, fewer hospital visits, more tertiary hospitals, fewer comorbidities (except for hypertension), and more thrombolytic therapy among statin-treated patients than nontreated patients (all p value < 0.05). For the intensity of statin therapy, 34,301 (55.1%) patients received low/moderate-intensity statin therapy, and 9133 (14.7%) received high-intensity statin therapy. Patients with high-intensity statin therapy had more comorbidities (especially hypertension and ischemic heart disease), hospital visits and medication use and fewer tertiary designated hospitals than patients with low/moderate-intensity statin therapy (all p value < 0.05).

Table 1. Baseline demographic and clinical characteristics of study participants, divided according to statin therapy.

Variable	No statin (n = 18,818)	Statin (n = 43,434)	*p* value	Low/moderate intensity (n = 34,301)	High intensity (n = 9133)	*p'* value
Age, year	68.94 (13.34)	64.41 (12.82)	<0.001	64.05 (12.83)	65.74 (12.67)	0.114
Female, %	6,076 (32.29)	11,944 (27.50)	<0.001	9,417 (27.45)	2,527 (27.67)	0.683
Number of visits/y	37.05 (41.73)	31.89 (37.72)	<0.001	31.32 (37.42)	34.03 (38.76)	<0.001
Tertiary designated hospital, %	10,989 (58.40)	28,695 (66.07)	<0.001	22,929 (66.85)	5,766 (63.13)	<0.001
CCI-index	1.10 (0.43)	1.06 (0.33)	<0.001	1.05 (0.31)	1.07 (0.38)	<0.001
Comorbidities, %						
Hypertension	14,955 (79.47)	34,888 (80.32)	0.014	27,257 (79.46)	7,631 (83.55)	<0.001
Previous TIA	511 (2.72)	838 (1.93)	<0.001	648 (1.89)	190 (2.08)	0.238
Atrial fibrillation	76 (0.40)	102 (0.23)	<0.001	72 (0.21)	30 (0.33)	0.037
Ischemic heart disease	470 (2.50)	978 (2.25)	0.062	714 (2.08)	264 (2.89)	<0.001
Congestive heart failure	103 (0.55)	88 (0.20)	<0.001	67 (0.20)	21 (0.23)	0.513
COPD	409 (2.17)	508 (1.17)	<0.001	387 (1.13)	121 (1.32)	0.120
Cancer	290 (1.54)	428 (0.99)	<0.001	313 (0.91)	115 (1.26)	0.003
Peripheral artery disease	69 (0.37)	157 (0.36)	0.921	109 (0.32)	48 (0.53)	0.003
Chronic liver disease	72 (0.38)	44 (0.10)	<0.001	30 (0.09)	14 (0.15)	0.079
Chronic kidney disease	131 (0.70)	137 (0.32)	<0.001	104 (0.30)	33 (0.36)	0.379
Discharge medications						
Antihypertensive	14,955 (79.47)	34,884 (80.31)	0.016	27,254 (79.46)	7,630 (83.54)	<0.001
Antiplatelet	15,825 (84.10)	41,254 (94.98)	<0.001	32,495 (94.73)	8,759 (95.90)	<0.001
Anticoagulants	7,710 (40.97)	16,686 (38.42)	<0.001	12,773 (37.24)	3,913 (42.84)	<0.001
NSAIDs	9,991 (53.09)	21,635 (49.81)	<0.001	16,648 (48.54)	4,987 (54.60)	<0.001
Thrombolytic	3,263 (17.34)	9,252 (21.30)	<0.001	7,243 (21.12)	2,009 (22.00)	0.068

CCI-index: Carlson comorbidity index; NSAIDs: nonsteroidal anti-inflammatory drugs.

Statin therapy and the risk of ICH readmission

Of the 62,252 participants, 628 ICH readmissions were recorded during a median follow-up of 3.17 years. Statin-treated patients had lower crude incidence rates of ICH than untreated patients (2.77 versus 3.24 per 1000 person-years), corresponding to a fully adjusted HR of 0.86 (95% CI, 0.73, 1.02; p = 0.089; Table 2). Compared with non-statin therapy, patients with low/moderate-intensity therapy had a lower risk of ICH (0.62: 0.52, 0.75), while patients with high-intensity therapy had a substantially higher risk (2.12: 1.72, 2.62; Table 2). The cumulative risk was higher in the high-intensity group than in the non-statin group throughout the follow-up period, while the risk was consistently lower in the low/moderate-intensity group ($p < 0.001$ for log-rank tests: Figure 1(a)). For patients with different types of statin therapy, adherence to rosuvastatin had the lowest risk of ICH compared to adherence to

Figure 1. Unadjusted Kaplan–Meier hazard curves for risk of intracranial hemorrhage readmission according to intensity and type of statin use: (a) shows the curves of ICH for the nonusers and low/moderate-intensity and high-intensity statin users and (b) shows the incidence curves for adherence to different types of statins.

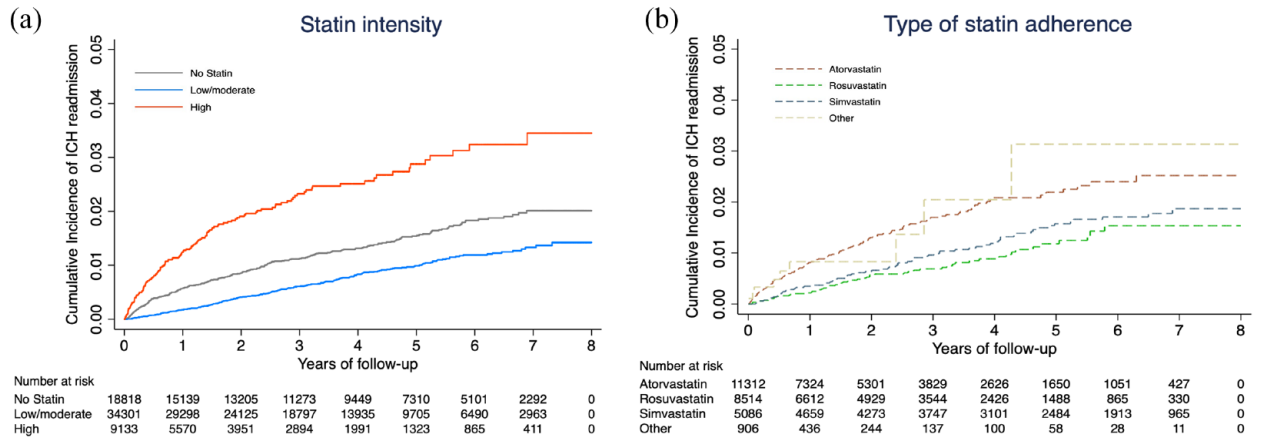
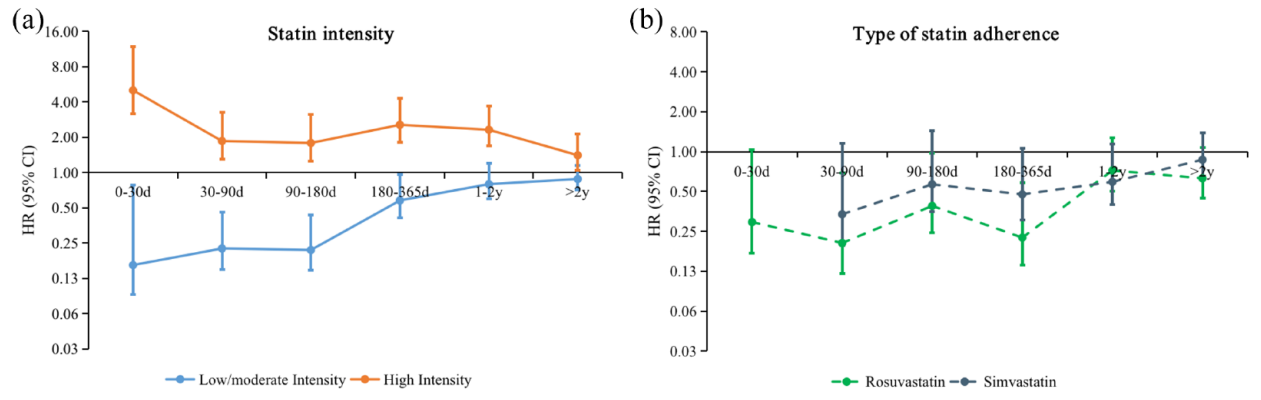


Figure 2. Hazard ratios of intracranial hemorrhage readmission associated with statin use after ischemic stroke at different times: (a) shows the HRs and 95% CIs of ICH for low/moderate-intensity and high-intensity statin users compared with nonusers; (b) shows the HRs and 95% CIs for adherence to rosuvastatin and simvastatin compared with atorvastatin.



atorvastatin (0.46: 0.34, 0.63), followed by simvastatin (0.60: 0.45, 0.81; Table 3), which was further confirmed by the cumulative incidence curve ($p < 0.001$ for log-rank tests: Figure 1(b)). Accounting for competing risks for death did not alter the results of the Cox proportional hazards model in all of the above analyses. The effects of statins were of limited duration and had a greater impact on ICH in the short term than in the long term after IS. Compared with patients who did not take statins, the protective effect on ICH disappeared 1 year after baseline in the low/medium-intensity statin-treated group, whereas high-intensity statin therapy was not associated with ICH risk 2 years later (Figure 2(a)). Similarly, adherence to different types of statins varied in ICH effects in the short period after stroke but tended to be consistent over longer periods (Figure 2(b)).

Subgroup analyses showed that statin therapy was associated with a slight reduction in the risk of ICH in men (0.80: 0.66, 0.97), patients with more than two visits in the previous year (0.76: 0.66, 0.95), or patients receiving thrombolytic therapy (0.70: 0.48, 0.99; Supplementary Table 1). After we matched the treated and nontreated groups by statin use throughout the follow-up after baseline, we obtained treated and nontreated patients with nearly identical characteristics (SMD < 0.1; Supplementary Table 2). As in the previous analysis, there was no difference in ICH risk between the treated group and the nontreated group (0.85:0.63, 1.15; $p = 0.299$; Supplementary Table 3), with an increased risk for high-intensity therapy (2.20: 1.45, 3.32) and a decreased risk for low/moderate-intensity therapy (0.63: 0.44, 0.89). In other sensitivity analyses, further exclusion of subarachnoid hemorrhage as an outcome (0.86: 0.72, 1.01), patients

Table 2. Hazard ratios of hemorrhagic stroke readmission after ischemic stroke discharge associated with statin therapy.

			HR (95% CI)	
	Total	Cases/PYs (/1000)	Cox regression model	Competitive risk model
No statin	18,818	3.24	Reference	Reference
Statin	43,434	2.77	0.86 (0.73, 1.02)	0.89 (0.75, 1.06)
Low/moderate intensity	34,301	1.97	0.62 (0.52, 0.75)	0.65 (0.54, 0.79)
High intensity	9133	7.38	2.12 (1.72, 2.62)	1.99 (1.61, 2.45)

HR: hazard ratio; CI: confidence interval.

Table 3. Hazard ratios of hemorrhagic stroke readmission after ischemic stroke discharge associated with type of statin adherence.

			HR (95% CI)	
Type of statin adherence	Total	Cases/PYs (/1000)	Cox regression model	Competitive risk model
Atorvastatin	11,312	5.24	Reference	Reference
Rosuvastatin	8514	2.40	0.46 (0.34, 0.63)	0.50 (0.37, 0.68)
Simvastatin	5086	2.84	0.60 (0.45, 0.81)	0.65 (0.49, 0.87)
Other	906	6.40	1.07 (0.54, 2.11)	1.00 (0.51, 1.96)

HR: hazard ratio; CI: confidence interval.

with atrial fibrillation (0.86: 0.73, 1.03), and patients receiving thrombolytic therapy (0.89: 0.74, 1.07) did not significantly alter risk estimates (Supplementary Tables 4–6). Competition for other cardiovascular outcomes did not offset the effect of low/moderate-intensity (0.61: 0.50, 0.73) and high-intensity (1.82: 1.48, 2.25) statins on ICH (Supplementary Table 7).

Discussion

This study leveraged medical insurance registers of the Chinese megacity to describe the association of statin therapy with hemorrhagic transformation after a first-time IS diagnosis from multiple perspectives. High-intensity statin therapy was associated with a higher risk of ICH, whereas low/moderate-intensity statin therapy showed a protective effect. Regarding the type of statin, adherence to rosuvastatin had the lowest risk compared with atorvastatin, followed by simvastatin.

Statin therapy is fairly common in populations with prior IS, but whether it causes cerebral hemorrhage transformation was controversial in the past. Our findings showed that statin use was not associated with ICH risk in all patients regardless of dose, consistent with 2 previous large cohort studies[6,7] and the majority of randomized controlled trials.[24] However, further results suggested that the association may differ depending on the intensity of treatment. Low/moderate-intensity post-IS statin therapy (considered the routinely recommended dose) reduced the risk of ICH by nearly 40%, which may support a previous Danish national cohort study advocating that any statin use after IS reduced the risk of ICH by half.[8] Our sensitivity analysis defined statin therapy and matched the control group in the same way as this previous study and still found protective effects only in the low-to-moderate-intensity statin group rather than in the full population, probably because of differences in statin dosage in the two study populations.

Of concern, we found that high-intensity statin therapy more than doubled the risk of ICH, supporting the results of a previous small-sample cohort study[9] and several randomized trials.[3,25] In contrast to the previous American Heart Association recommendation for intensive statin therapy in stroke patients younger than 75 years of age,[26] the US Preventive Services Task Force's latest review recommend selective prescribing of moderate-intensity statin therapy based on cardiovascular risk factors in adults 40–75 years of age, while insufficient evidence was available for adults ⩾76 years of age.[27] Our findings of adverse effects of high-dose statin therapy provide further evidence to this recommendation. In addition, high-intensity statin use was found to be more associated with short-term than long-term risk of ICH after IS, underscoring a critical period for ICH prevention in patients with this type of therapy.

The opposite association between different intensities of statin therapy and the risk of ICH in patients with IS may be

explained by conflicting underlying biological mechanisms. On one hand, statins were found to reduce oxidative stress and inflammation, improve endothelial function, and stabilize atherosclerotic plaques, thereby potentially reducing the propensity of hemorrhage.[28] Therefore, it is likely that these protective effects of statins play a major role in the low/moderate-intensity group. On the other hand, high-intensity statin therapy has exceeded the recommended dose, possibly leading to some potentially risky effects. Some studies have confirmed that the cholesterol-lowering effect of statins is associated with an increased risk of ICH.[29] In particular, a Mendelian randomization study of Chinese adults demonstrated an inverse causal association of low-density lipoprotein cholesterol with ICH.[30] Other pleiotropic effects of statins could also theoretically contribute to the hemorrhagic risk, for example, inhibiting platelet aggregation, enhancing fibrinolysis, and thus reducing thrombosis.[31,32] In addition, statins have been reported to cause arterial muscle necrosis and microaneurysm formation, thus leading to hemorrhage.[33]

Our study showed the different effects of different types of statin therapy in patients with prior IS. Specifically, adherence to rosuvastatin or simvastatin was associated with a lower risk of ICH than atorvastatin, with rosuvastatin therapy having the lowest risk. To our knowledge, most previous studies have only compared atorvastatin and/or rosuvastatin, and few studies have compared the efficacy of multiple statins in patients with IS.[5] Despite the lack of evidence in patients with IS, our finding is consistent with the result of a previous randomized controlled trial in those with an ICH as an entry event, which found that ICH was more frequent in patients treated with atorvastatin.[34] In other clinical studies, rosuvastatin has also shown better performance than atorvastatin in reducing serum low-density lipoprotein cholesterol (LDL-C) and clinical efficacy.[11,13] This may be explained by the theoretical lower ability of hydrophilic statins to cross the blood–brain barrier.[35]

To the best of our knowledge, this study is the largest to assess the association of statin use with incident ICH in an Asian population, with new IS as the entry event. We used a retrospective cohort study based on Medicare data covering an entire megacity to explore the association from multiple perspectives, including statin dose and type. To avoid the impact of a history of lipid-lowering drug use before stroke on ICH and the resulting population differences in baseline conditions, we excluded patients who had used lipid-lowering drugs 1 year before the diagnosis of IS. After adjusting for multiple confounders and sensitivity analyses, we found fairly stable results that statin therapy after IS did not increase the risk of ICH overall, except for high-intensity therapy. Given the other substantial cardiovascular benefits of statins, our study highlights that the risk of ICH in patients with IS should not be negligible with high-dose statin therapy but does not argue against low/moderate-intensity statin therapy. The risk of ICH with different types of statins was evaluated for the first time in patients with IS in this study, suggesting the possibility of switching statin types in stroke treatment to reduce the risk of adverse effects of statin therapy.

There are some limitations to this study that are worth discussing. First, although Medicare's database had objectively and accurately recorded every participant's prescription payment, drug prescriptions did not necessarily reflect patients' actual medication use. The fact that the actual dose due to insufficient medication adherence was less than the recorded dose may bias our risk estimates for the high-dose group toward null hypothesis. Second, the use of statins may be related to the subjects' serum cholesterol levels at baseline, leading to an inversion of cause and effect. Therefore, we minimized this bias by excluding patients with a history of lipid-lowering medications at baseline and adjusting or matching for baseline hyperlipidemia. Third, statin use at baseline may not reflect long-term statin use, but more than 83% of statin users start statin use within 1 month after IS. Using drug use within 1 month after the initial diagnosis resulted in more consistent courses of IS among the subjects. To discuss whether subsequent changes in statin use altered the results, we explored any statin use throughout follow-up in a sensitivity analysis and obtained the same results. Fourth, statin users changed the type of statin they used during follow-up, with fewer using a single type of statin. Therefore, to compare the differences in statin types, only patients adhering to a single type of statin were selected for discussion, and transient use of other types of statins was ignored. Fifth, the lack of information on lifestyle, biochemical markers (lipoprotein level, blood pressure control), and genetics in health care data limits further exploration of these factors. Sixth, ICH due to secondary causes or trauma cannot be ruled out because the Medicare database lacks detailed information on each individual's medical history. Therefore, more detailed clinical data are needed to further explore the risk of ICH under different etiologies.

In conclusion, our study shows that the risk of ICH in patients with IS was not consistent across intensives and types of statin therapy. High-intensity statin use increased the risk of readmission for ICH, while low/moderate-intensity statin therapy showed a protective effect. Compared with atorvastatin, adherence to rosuvastatin had the lowest risk of ICH, followed by simvastatin. We support low/moderate-intensity statin therapy after IS, avoiding high-intensity statin use and choosing low-risk statin types to avoid the risk of ICH.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by the National Natural Science Foundation of China (grant nos. 81703291 and 81872695) and the China Postdoctoral Science Foundation (grant no. 2022TQ0017).

Ethics approval and consent to participate

This study is considered exempt from institutional review board approval since the data used were collected for administrative purposes without any personal identifiers. The data were collected for an administrative purpose without any personal identifiers; therefore, the study was exempted from the informed consent statement.

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Supplemental material

Supplemental material for this article is available online.

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Received: 24 April 2023 | Accepted: 26 April 2023

DOI: 10.1111/1753-0407.13408

Journal of Diabetes WILEY

LETTER TO THE EDITOR

Response to: Critical commentary on the association between thiazolidinedione use and dementia risk in patients with type 2 diabetes

We thank Wasif et al for their comments[1] on our article that explored the association between thiazolidinedione (TZD) use and dementia risk in patients with type 2 diabetes mellitus (T2DM).[2] In their letter, the authors addressed the potential confounding effects of age of diabetes onset and mental disorders, which were suggested to be associated with dementia risk in recent studies,[3,4] and thus they suggested subgroup analyses according to participants' age at T2DM onset and status of mental disorders.[1] In our analyses we controlled age and years of T2DM at baseline[2]; thus the issue of collinearity would arise in the multivariate and inverse probability weighted model if we controlled age of T2DM onset, which was the difference between baseline age and diabetes duration. Moreover, comorbidities were adjusted using the Charlson comorbidity index, which did not contain mental disorders.[2]

In response to the authors' concerns, we conducted subgroup analyses according to their suggestions[1] (Table 1). Age of diabetes onset was defined as the age when the patient was first diagnosed with T2DM. In addition, history of mental disorders was identified using the *International Classification of Diseases, Tenth Revision* (all codes of F10–F99 except F70–F79) according to a previous study.[4] Consistent with previous studies, we observed higher incidence of dementia in patients of older age and with history of mental disorders.[3,4] But no significant effect modification was observed. Compared with use of alpha-glucosidase inhibitors, TZD use was significantly associated with dementia incidence in different age groups, with a hazard ratio (HR) of 0.44 (95% confidence interval [CI], 0.21–0.91), 0.62 (95% CI, 0.39–0.98), and 0.47 (95% CI, 0.31–0.71) for T2DM patients aged <55 years, 55–65 years, and >65 years, respectively. Similarly, TZD use was consistently associated with dementia risk in terms of history of mental disorders, with an HR of 0.53 (95% CI, 0.30–0.94) and 0.50 (95% CI, 0.36–0.69) for T2DM patients with and without history of any mental disorders, respectively.

We agree with the authors that we cannot fully rule out biases caused by unmeasured confounding and inaccurate information.[5] Therefore, we conducted several sensitivity analyses using different dementia identification rules combing diagnosis and prescriptions of antidementia drugs. Results under various outcome definitions were consistent (the Table 1), suggesting that our results were robust against potential outcome misclassification.[2] Furthermore, we did not adjust full medication history and some other potential confounders, such as dietary patterns, hence we calculate the E-value as a sensitivity analysis. The E-value for the observed HR of 0.51 in our primary analysis was 3.33, which was the minimum strength that an unmeasured confounder needed to be associated with both the exposure and outcome to explain away the observed association.[2]

However, our analyses should be interpreted in the context of its observational nature. Future prospective studies with more refined measurement of dementia cases and potential confounders are needed to give further insights into the potential role of TZDs in reducing dementia incidence.

AUTHOR CONTRIBUTIONS

Houyu Zhao conceived of and designed the work. Hongbo Lin, Peng Shen, and Yexiang Sun acquired the data. Houyu Zhao analyzed the data. Houyu Zhao drafted the manuscript. Lin Zhuo and Siyan Zhan critically revised the manuscript for important intellectual content. Siyan Zhan, Hongbo Lin, and Peng Shen supervised the study. Houyu Zhao and Siyan Zhan obtained the funding. All authors were responsible for the interpretation of the data, and revised, and gave final approval of the manuscript. Siyan Zhan is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

TABLE 1 Association between TZD use and incidence of dementia stratified by age at T2DM diagnosis and mental disorder under different outcome definitions.

	AGI users		TZD users		
Subgroup analyses	**Cases/PY**	**Incidence (/100 000 PY)**	**Cases/PY**	**Incidence (/100 000 PY)**	**HR (95% CI)**
Primary outcome definition[a]					
Age at T2DM diagnosis					
<55	94/129415	72.6	9/37280	24.1	0.44 (0.21–0.91)
55–65	152/93546	162.5	24/26997	88.9	0.62 (0.39–0.98)
>65	307/59597	515.1	27/12471	216.5	0.47 (0.31–0.71)
Any mental disorder					
No	415/231879	179.0	45/62197	72.4	0.50 (0.36–0.69)
Yes	138/50678	272.3	15/14551	103.1	0.53 (0.30–0.94)
Outcome definition 2[b]					
Age at T2DM diagnosis					
<55	92/129365	71.1	9/37273	24.1	0.45 (0.22–0.93)
55–65	149/93462	159.4	22/26990	81.5	0.59 (0.37–0.96)
>65	303/59385	510.2	27/12404	217.7	0.48 (0.32–0.72)
Any mental disorder					
No	407/231583	175.7	44/621146	70.8	0.50 (0.36–0.69)
Yes	137/50629	270.6	14/14521	96.4	0.52 (0.29–0.93)
Outcome definition 3[c]					
Age at T2DM diagnosis					
<55	62/129421	47.9	5/37282	13.4	0.32 (0.12–0.83)
55–65	99/93590	105.8	13/27006	48.1	0.54 (0.29–1.01)
>65	189/59652	316.8	16/12426	128.8	0.44 (0.26–0.75)
Any mental disorder					
No	263/231917	113.4	26/62178	41.8	0.46 (0.30–0.71)
Yes	87/50747	171.7	8/14536	55.0	0.39 (0.18–0.87)
Outcome definition 4[d]					
Age at T2DM diagnosis					
<55	101/129356	78.1	11/37264	29.5	0.48 (0.25–0.93)
55–65	166/93444	177.6	28/26961	103.9	0.64 (0.42–0.98)
>65	327/59388	550.6	29/12403	233.8	0.46 (0.31–0.68)
Any mental disorder					
No	445/231582	192.2	49/62129	78.9	0.50 (0.37–0.68)
Yes	149/50606	294.4	19/14500	131.0	0.56 (0.33–0.93)
Outcome definition 5[e]					
Age at T2DM diagnosis					
<55	143/129255	71.6	18/37242	48.3	0.58 (0.34–0.98)
55–65	226/93315	189.9	40/26932	148.5	0.68 (0.47–0.98)
>65	490/59122	603.4	57/12368	460.9	0.59 (0.44–0.78)
Any mental disorder					
No	648/231230	280.2	81/62063	130.5	0.57 (0.45–0.73)
Yes	211/50463	418.1	34/14477	234.8	0.73 (0.51–1.08)

Abbreviations: AGI, alpha-glucosidase inhibitor; CI, confidence interval; HR, hazard ratio; PY, person years; TZD, thiazolidinedione; T2DM, type 2 diabetes mellitus.

[a]An incident dementia case was defined as (a) having at least two consecutive diagnosis code or description of F00–F03 or G30, or (b) having at least one dementia diagnosis record and prescription records of antidementia drugs. Details of outcome definitions have been published previously.[2]

[b]Outcome definition 2: Dementia defined as having at least two diagnoses of F00–F03 or G30;

[c]Outcome definition 3: Dementia defined as having over two diagnoses of F00–F03 or G30 and prescriptions of antidementia agents after the first diagnosis;

[d]Outcome definition 4: Dementia defined as having a consecutive diagnosis of F00–F03 or G30 or prescription of antidementia agents within 1 year of the first diagnosis of dementia;

[e]Outcome definition 5: Dementia defined as any diagnosis of F00–F03 or G30.

FUNDING INFORMATION

This work was supported by a grant from the China Postdoctoral Science Foundation (Grant No. 2022M710251) and a grant from the National Natural Science Foundation of China (Grant No. 81973146). The funder had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the article for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the article for publication.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Shen *et al.*
BMC Medical Research Methodology (2023) 23:130
https://doi.org/10.1186/s12874-023-01954-0

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Robust estimation of dementia prevalence from two-phase surveys with non-responders via propensity score stratification

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Abstract

Background Missing diagnoses are common in cross-sectional studies of dementia, and this missingness is usually related to whether the respondent has dementia or not. Failure to properly address this issue can lead to underestimation of prevalence. To obtain accurate prevalence estimates, we propose different estimation methods within the framework of propensity score stratification (PSS), which can significantly reduce the negative impact of non-response on prevalence estimates.

Methods To obtain accurate estimates of dementia prevalence, we calculated the propensity score (PS) of each participant to be a non-responder using logistic regression with demographic information, cognitive tests and physical function variables as covariates. We then divided all participants into five equal-sized strata based on their PS. The stratum-specific prevalence of dementia was estimated using simple estimation (SE), regression estimation (RE), and regression estimation with multiple imputation (REMI). These stratum-specific estimates were integrated to obtain an overall estimate of dementia prevalence.

Results The estimated prevalence of dementia using SE, RE, and REMI with PSS was 12.24%, 12.28%, and 12.20%, respectively. These estimates showed higher consistency than the estimates obtained without PSS, which were 11.64%, 12.33%, and 11.98%, respectively. Furthermore, considering only the observed diagnoses, the prevalence in the same group was found to be 9.95%, which is significantly lower than the prevalence estimated by our proposed method. This suggested that prevalence estimates obtained without properly accounting for missing data might underestimate the true prevalence.

Conclusion Estimating the prevalence of dementia using the PSS provides a more robust and less biased estimate.

Keywords Prevalence estimation, Missing data, Propensity score

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Background

Dementia is a neurodegenerative disease that leads to irreversible memory loss, language dysfunction, and difficulties in carrying out daily activities [1]. In an aging society, dementia has become a major public health challenge, affecting nearly 50 million people worldwide [2, 3]. This places a heavy burden not only on people with dementia and their families, but also on society and the economy. The total cost of caring for people with dementia is one of the largest healthcare expenditures for society, and is expected to reach $355 billion globally in 2021 [4]. China is also expected to spend $507.49 billion on dementia care in 2030 [5]. In addition, mild cognitive impairment (MCI), the intermediate state between normal and dementia, has also been the focus of research [1]. The number of people with dementia or MCI is increasing over time, leading to a growing healthcare burden in the future [6]. Therefore, an accurate prevalence estimation is essential to understand the disease, accurately assess the burden of disease, and make informed health policy decisions [6, 7].

Dementia research typically follows a two-phase survey approach [8]. In phase I, screening is carried out in the general population to identify high-risk participants, who then undergo systemic neuropsychological testing in phase II to obtain accurate diagnoses. However, there are significant challenges in conducting testing in phase II [9, 10]. Some of the essential tests are complex and can be difficult for participants with poor physical, hospitalization, and cognitive conditions to complete, leading to a high non-response rate in phase II [11]. This results in non-random missingness of final diagnoses and challenge to the estimation of dementia prevalence [12].

Missing data is a common issue in cross-sectional studies of dementia. Wu's meta-analysis showed that large-scale prevalence studies in China had a response rate of around 90% [13]. However, traditional methods of dealing with missing data involve simply removing non-responders' data points from the analysis, which can lead to an underestimation of prevalence. This is particularly true for studies of dementia, as missing diagnoses in phase II are more likely to be associated with higher disease rates. In these cases, the missing mechanism is classified as missing not at random (MNAR) [14].

Unfortunately, we have found that many previous studies suffer from the defect of not properly dealing with missing data, resulting in underestimates of the prevalence and burden of dementia [15, 16]. For example, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) calculated global prevalence through systematic reviews without correcting the potential bias due to missing data [4, 6]. In recent years, many researchers have made great efforts to address this critical issue. Tan et al. [17] proposed to impute the missing diagnoses in phase II via various imputation methods and compared the resulting estimated prevalence. There are some previous studies that have dealt with missing data in different ways in longitudinal studies [18–20], but not in cross-sectional studies. Chen developed a method called the Diggle-Kenward (DK) selection model to deal with MNAR [21]. However, there is still a lack of a logical strategy with an explicit protocol to properly handle the unobserved diagnoses that are MNAR in the field of dementia research.

In recent years, propensity scores (PS) have gained popularity in observational studies. Defined as the conditional probability of a unit being assigned to a particular treatment group given a set of observed covariates, PS can help balancing confounding factors across treatment or exposure groups [22]. We assume that when the observed indicators are included to build non-response PS model, the composition of independent variables in the model help us to diagnose the existence of MNAR. It will indicate MNAR, if the meaningful independent variables contain those associated with the outcome. In such cases, direct estimation, also known as marginal effects, may be influenced by several confounding factors.

In this study, we have addressed the challenge of handling missing data under the MNAR mechanism by introducing a general strategy using propensity score stratification (PSS) [22]. Within the stratification, the observed and missing data can be approximated as identically distributed, making it a conditional effects method. By applying the proposed strategy to estimate the prevalence of dementia among male veterans enrolled in the Chinese Veteran Clinical Research (CVCR) platform, we obtained an unbiased prevalence estimator that is robust to different imputation methods.

Methods

Data source

This study was based on a sub-project of the Chinese Veteran Clinical Research (CVCR) Platform for the Assessment of Non-Communicable Diseases program. It was a multicenter, two-phase, cross-sectional study to estimate the prevalence of dementia and MCI. The design and protocol of the CVCR have been approved by the Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital(No. 20090820–02) [23]. In this study, we reviewed the de-identified database of the CVCR platform, and the design and protocol of data analysis were approved by Ethics Committee of the Peking University Third Hospital (No. M2016114 and M2017055).

Study population

The CVCR survey included 8,246 veterans aged 60 and over from 277 veteran communities in 18 cities who had registered on the CVCR platform and had been living continuously in a veteran community for at least one month. Of the 8,246 veterans who participated in the survey, $n_I = 3,801$ were diagnosed as normal in phase I, and only the remaining $n_{II} = 4,445$ were enrolled in phase II. Among the participants enrolled in phase II, 1,170 failed to complete enough neuropsychological batteries to obtain a clinical diagnosis and were defined as non-responders, while the others received a specific diagnosis (589 normal, 1979 MCI, 707 dementia). Figure 1 illustrates the main results in both phases of the survey, and detailed baseline characteristics of the participants are shown in Table 1.

Diagnostic criteria

The Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE) and the Activities of Daily Living (ADL) scale were used in the phase I to assess participants' cognitive and physical conditions [24]. Socio-demographic data (age, gender, education and

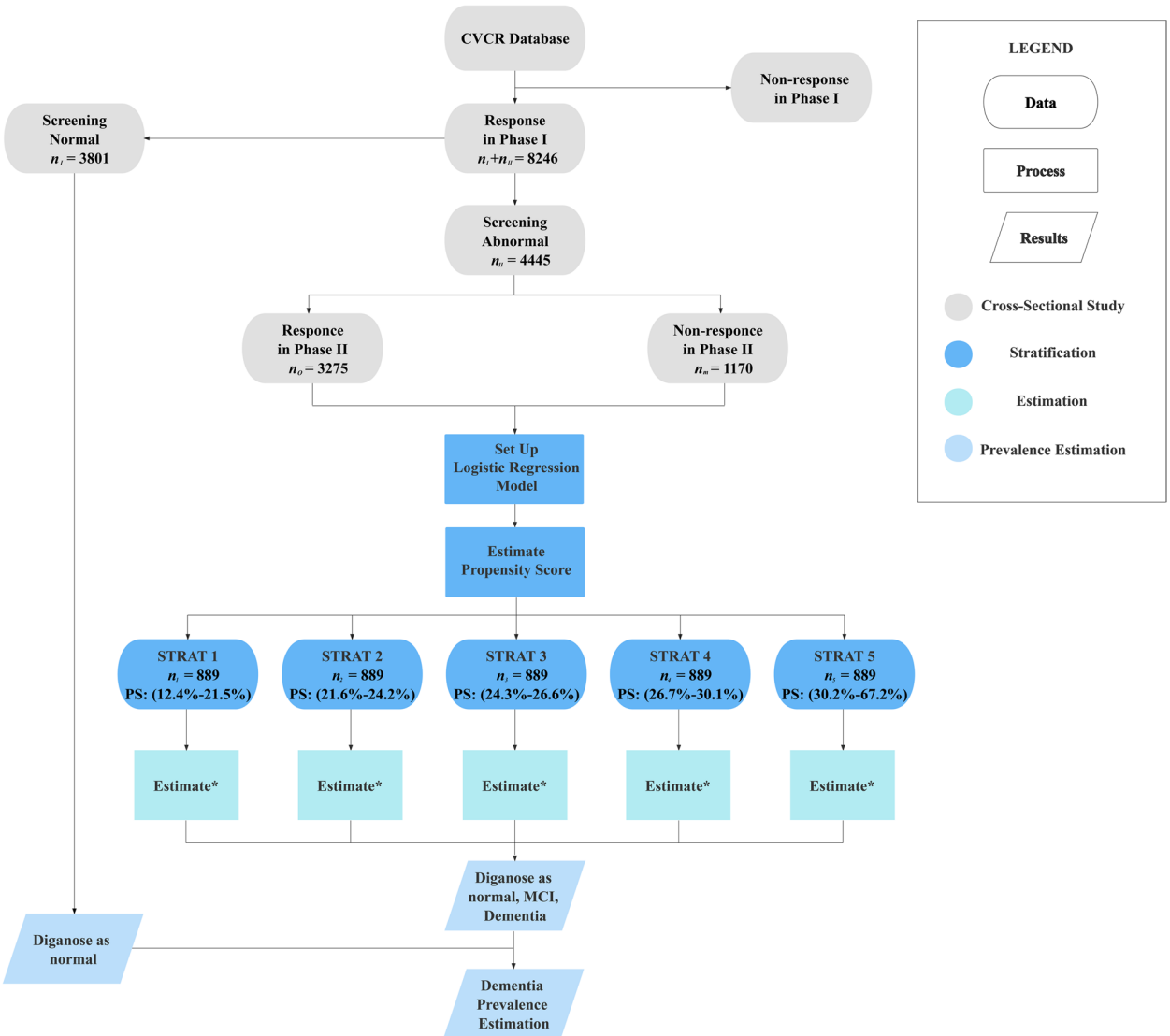

Fig. 1 Schematic diagram of imputation and propensity score in each stratum * Estimation methods included simple estimation, regression estimation, and regression estimation with multiple imputation. Each stratum was imputed in the same way and the estimations were then combined. The covariates used by regression estimation were different at each stratum. Note: Propensity score for non-response was calculated by logistic regression

Table 1 Baseline characteristics of the sub-population with and without diagnosis in phase II

	Sub-population with diagnosis ($n=3275$)	Sub-population without diagnosis ($n=1170$)	*P*-value	SMD
Age,	82.89 ± 3.72	83.08 ± 3.76	0.14	0.05
Year of Education	7.52 ± 4.58	7.55 ± 4.76	0.86	0.01
PADL score	12.25 ± 5.01	13.01 ± 6.00	< 0.001	0.14
IADL score	15.28 ± 8.74	15.86 ± 9.29	0.06	0.06
MMSE score	24.91 ± 5.16	24.15 ± 5.02	< 0.001	0.15
MoCA score	21.48 ± 5.56	20.00 ± 5.21	< 0.001	0.27

Data are expressed as mean ± SD

Abbreviations: *SMD* standardized mean difference, *MoCA* Montreal Cognitive Assessment, *MMSE* Mini-Mental State Examination, *PADL* physical activities of daily living, *IADL* Instrumental activities of daily living. *P*-values were calculated using t-test or Wilcoxon signed-rank test, depending on the distribution of covariates. A two-tailed *P*-value < 0.05 was considered statistically significant. The PADL score, MMSE score, and MoCA scores of the two sub-populations were significantly different in the sense that the *P*-value was less than 0.05, a result that still holds after Bonferroni correction

living conditions) were collected by the investigators in a face-to-face interview.

In phase II, systemic neuropsychological tests were used to assess memory, language, visuospatial perception, calculation, abstract reasoning and executive function. Clinical diagnoses were made on the basis of a joint consideration of the patient's medical history, systematic neuropsychological tests, physical examinations in internal medicine and neurology, head CT or MRI, and blood tests. The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) [25]. The core clinical criteria was recommended by the International Aging and Alzheimer's Disease Association to diagnose MCI [26].

Statistical analysis

The characteristics of responders and non-responders in phase II were described by the mean (± standard deviation). The results obtained from these analyses, as shown in Table 1, reveal significant differences between responders and non-responders in phase II, suggesting that the corresponding missing mechanism is obviously missing not at random (MNAR). The following analysis consists of three parts: setting up the PS model and stratification, estimating stratum-specific prevalence, and summarising for final estimation. The analysis protocol is shown in Fig. 1 with the specific analysis process and formulas detailed in the supplementary material.

Non-random missing responses pose a critical challenge to prevalence estimation in practice and may lead to biased results if not handled properly. In this study, we address this issue by recommending the use of propensity score stratification (PSS) framework [22]. The propensity score (PS) was used to assess the missing probability of diagnostic results for those who entered phase II. Logistic regression is commonly used to calculate propensity scores (PSs), with the response variable being whether the participant has a missing diagnosis. The independent variables in the regression model can first include all variables related to dementia, such as socio-demographic information and cognitive screening scores, and then use stepwise regression to filter out the significant variables. We can then simply partition all participants into 5 equally sized strata based on the quintiles of the empirical distribution of the estimated propensity score. Rosenbaum and Rubin (1983) showed that such a strategy leads to simplified unit stratifications, within each of which the unobserved responses are approximately missing at random (MAR).

Based on the stratification approach, we can estimate the prevalence of each stratum using two different estimation methods: simple estimation (SE) and regression estimation (RE). SE directly estimates the prevalence of each stratum by calculating the percentage of dementia among the responders in the stratum. Since the prevalence estimator follows a binomial distribution, its variance can be easily estimated. On the other hand, RE utilizes an ordered logistic regression model between the covariates $\boldsymbol{X}$ and the response $\boldsymbol{Y}$ to provide a more statistically efficient prevalence estimation with a smaller estimation variance. In contrast to the calculation of propensity scores, the responses in RE are ordinal variables with three categories: normal, MCI and dementia. Similarly, we first consider the full set of covariates in each stratum and then filter out the significant variables by stepwise regression, with possible differences in the final covariates used in each stratum. In addition, we can combine multiple imputation, which is a Bayesian method for imputing missing data multiple times, with the aforementioned estimation methods. In this study, we utilized regression estimation with multiple imputation (REMI) to estimate the prevalence of each stratum [12]. Specifically, we followed the concept of regression estimation in modeling each stratum, but employed a

Bayesian approach to impute missing values. As a result, after several imputations, different versions of the complete dataset can be obtained for each stratum. We then pool the prevalence estimates from each dataset to obtain a final stratum-specific prevalence.

Given the stratum-specific prevalence estimates, we integrate them into a proper estimate of overall prevalence via a weighted average, where the weight of each stratum is proportional to the sample size within it. The main advantage of such a stratification-based strategy is that, after stratification, the missing responses within each PSS can be treated approximately as MAR, making it logically sound and technically convenient for statistical inference on the unknown prevalence.

All analyses were performed using R (version 4.0.2). Details can be found in Supplementary Material.

Results

Propensity score stratification and baseline characteristics in each stratum

To establish a proper PSS for participants in phase II of the CVCR survey, we built a logistic regression model to describe how a participant's response rate varies with their covariates. The parameters of the model could be estimated using the observed indicators of responders and non-responders as responses. For each participant with a given set of covariates, their propensity score, derived from the fitted regression model, represents the predicted probability of them being a non-responder. Initially, we considered all recorded covariates that could potentially be associated with the absence of a diagnosis in the logistic regression, including sociodemographic information (e.g., age and year of education) and cognitive screening scores (e.g., MoCA, MMSE, and ADL). We gradually removed unimportant variables using stepwise regression with AIC as the model selection principle, resulting in a final model with only 4 covariates:

$$\log\left(\frac{PS}{1-PS}\right) = -0.56 - 0.08MoCA + 0.04MMSE + 0.03PADL - 0.02IADL.$$

Figure 2A shows the distributions of estimated PSs for both responders and non-responders, with non-responders on average had higher PSs than responders. A Wilcoxon test was performed to confirm that the difference between the two PS distributions was statistically significant (P-value < 0.001). It is important to note that if the missing mechanism was MAR, there will not be a meaningful PS model based on variables related to dementia itself. At the same time, the risk of non-response calculated by such a model could not effectively distinguish non-response from response patients. This finding is consistent with our prior knowledge that the missing mechanism in phase II of the CVCR survey involvesmissing not at random (MNAR), which supports the need for a propensity score stratification framework to adequately address missingness in dementia surveys.

To stratify all participants based on quintiles of estimated propensity scores, we divided the range of all estimated propensity scores into five strata, with the same number of participants in each stratum. The stratum boundaries are indicated by red dashed lines in Fig. 2A. The PSs of stratum 1 to 5 range from low to high, representing a low to high risk of missing a diagnosis. Importantly, there were enough responders and non-responders in all five strata to ensure that we had enough information to estimate the prevalence within each stratum.

We observed that the proportion of normal, MCI and dementia differed in each stratum (Fig. 2B). As the PS increased, the proportion of dementia and MCI in the observed data gradually increased. For example, the proportion of dementia in stratum 1 was 7.99%, compared with 33.85% in stratum 5. In addition, the proportion of non-responders also increased.

Figure 2 further shows the distributions of various covariates and estimated PSs in each of the 5 strata. It was clear that some covariates (such as MoCA score, MMSE score, etc.) had markedly different distributions across the strata. In particular, there was a clear linear trend between stratum and MoCA score ($P < 2.2 \times 10^{-16}$), as shown in Fig. 2F.

Prevalence estimation for strata and overall population

The prevalence of dementia and MCI estimated using SE, RE and REMI within each PSS is shown in Table 2. The estimation method was the same for both, except that the response variable $\boldsymbol{Y}$ was changed from dementia to MCI. We found that the prevalence estimated by the three methods was very consistent within each PSS. For example, in stratum 5, with the highest percentage of missing diagnoses (34.63%), the estimated prevalence of dementia by PSS-SE, PSS-RE, and PSS-REMI was 51.86%, 51.97% and 51.63%, respectively. Furthermore, the sum of the prevalence of MCI and dementia gradually increased from stratum 1 to stratum 5. The proportion of the normal population estimated by the PSS-RE in each stratum was 46.68%, 19.24%, 5.85%, 4.39% and 2.02%, respectively. This suggests that the higher the propensity score of the respondent, the higher the risk of cognitive impairment. In addition, the prevalence of MCI first increased and then decreased, being highest in stratum 3. This might be because the proportion of respondents with dementia increased rapidly in stratum 4 and 5, as presented in Fig. 2B.

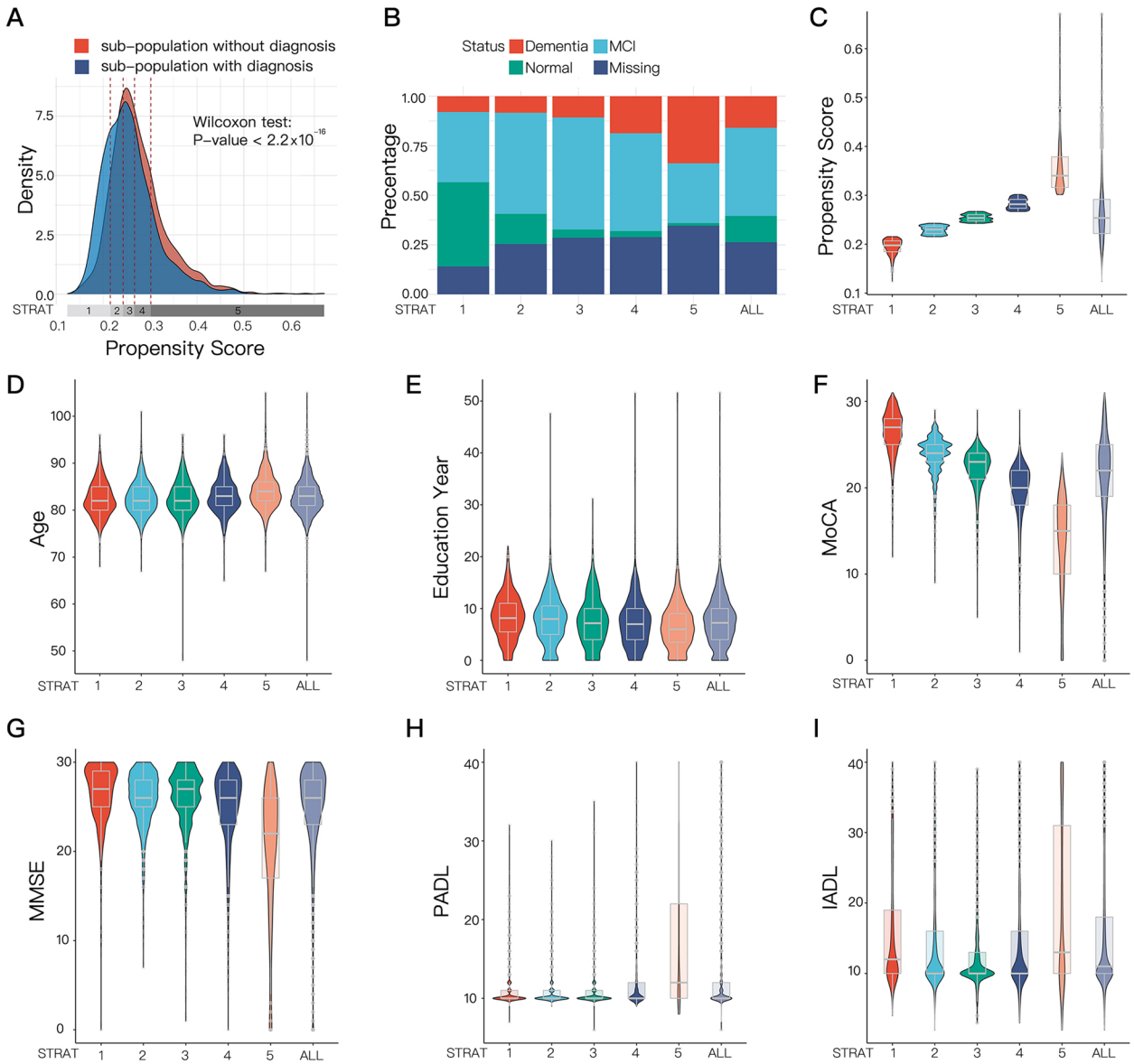

Fig. 2 Distribution of PS on sub-populations with and without a diagnosis (**A**), and diagnosis status, propensity score and covariates in each stratum (**B**-**I**). **A** Four red dotted lines represent the quintiles of the propensity score. Wilcoxon signed-rank test showed that the PSs were on average higher in the sub-populations without diagnosis (*P*-value < 0.001). **B**-**I** The X-axis of each graph is stratum 1 to 5, and all the data. Fig **B** represents the percentage of diagnosis status: dementia, MCI, normal and missing. Fig **C**-**I** represent the distribution of PS score (**C**), age (**D**), year of education (**E**), PADL score (**F**), IADL score (**G**), MMSE score (**H**), MoCA score (**I**) in each stratum

Figure 3 visualizes the estimated prevalence and corresponding 95% confidence intervals for the whole population ($n_I + n_{II}$ participants) based on different estimation methods using PSS (red intervals), as well as the results without PSS (purple intervals). Under the PSS framework, the prevalence and corresponding intervals obtained by the three estimation methods are highly consistent, indicating that all three methods effectively impute missing data and estimate prevalence when the missing mechanism within each stratum is MAR. However, on an unstratified basis, where the essential requirement for dealing with missing data is not met, the estimated prevalence of the different methods differs significantly and the confidence intervals of the SE and RE do not even overlap. Furthermore, RE, which uses information on covariates, can partially counteract the effect of MNAR mechanisms in the data, leading to similar results as the PSS-based approach. However, it is

Table 2 Estimated percentage of participants with different cognitive status within each PSS, phase II and CVCR

		STRAT 1 (%) ($n_1 = 889$)	STRAT 2 (%) ($n_2 = 889$)	STRAT 3 (%) ($n_3 = 889$)	STRAT 4 (%) ($n_4 = 889$)	STRAT 5 (%) ($n_5 = 889$)	phase II (%) ($n_{II} = 4445$)	CVCR (%) ($n_I + n_{II} = 8246$)
PSS-SE	MCI	41.28 (0.62)	68.5 (0.79)	79.19 (0.73)	69.52 (0.83)	46.12 (0.98)	60.90 (0.36)	32.83 (0.19)
	dementia	9.34 (0.37)	11.14 (0.53)	14.96 (0.64)	26.32 (0.79)	51.86 (0.99)	22.70 (0.31)	12.24 (0.17)
PSS-RE	MCI	43.31 (0.61)	68.95 (0.73)	79.98 (0.65)	69.74 (0.75)	46.01 (0.80)	61.60 (0.32)	33.20 (0.17)
	dementia	10.01 (0.41)	11.81 (0.47)	14.17 (0.52)	25.87 (0.68)	51.97 (0.78)	22.79 (0.26)	12.28 (0.14)
PSS-REMI	MCI	43.19 (0.63)	69.18 (0.83)	79.64 (0.72)	69.97 (0.83)	46.34 (0.93)	61.69 (0.36)	33.25 (0.19)
	dementia	9.79 (0.41)	11.36 (0.52)	14.51 (0.61)	25.76 (0.78)	51.63 (0.91)	22.63 (0.30)	12.20 (0.16)

Data are expressed as mean (standard deviation) of the percentage

Abbreviations: *STRAT* stratum

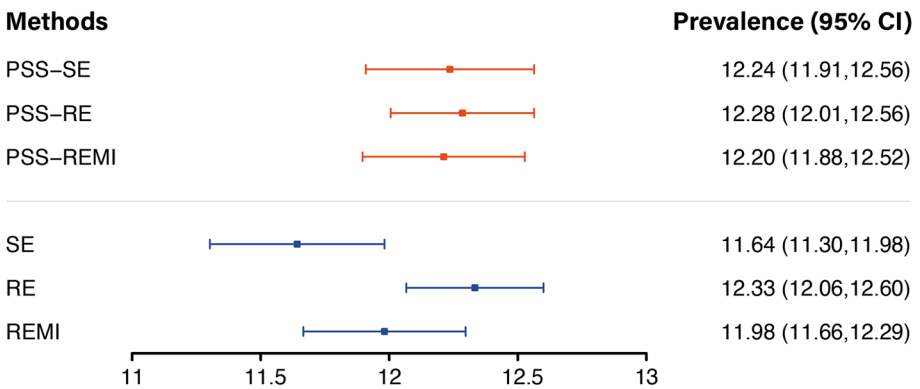

Fig. 3 Comparison of estimated prevalence of CVCR between three methods with and without PSS. Estimated prevalence using different imputation methods are expressed as mean (95% CI). The upper panel represents the results with PSS

important to emphasize that the direct use of RE is still very risky.

Compared with the prevalence of 9.95% before the treatment of missing data, the mean estimated prevalence under the PSS framework was 12.24%, suggesting that the true prevalence may have been underestimated in the past.

Compared the prevalence with published data by 80–89 age male

To compare the prevalence estimation with other studies, we chose the published data from Zhao et al. [27] and Jia et al. [28], which were large cross-sectional studies in China and could better represent the prevalence of dementia in China. The prevalence and the confidence interval were calculated from published second-hand data. The results were presented as a forest plot (Fig. 4). As the final prevalence was standardized differently and the 80–89 year old group had less weight in published studies, which was not the case for the CVCR where this age group had a larger population, we chose the 80–89 year old male group to calculate the prevalence for better comparability.

When comparing the group of men aged 80–89 years, the estimated prevalence of dementia in the CVCR was higher than in other dementia studies, as shown in Fig. 4. For older individuals aged 80–89 years, the prevalence of dementia in this study (12.29%) was similar to the prevalence estimated by the GBD for China in the same year (12.68%). In other individual studies conducted in China during the same period, the prevalence was lower than the GBD estimates (9.50% vs 11.82% for 1998 [27], 11.83% vs 13.89% for 2019/2020 [28]). In general, the prevalence of dementia in older people is gradually increasing over time, as shown by the trend in the GBD study.

Using PSS, the prevalence estimated by the three methods was approximately 14% in the 80–89 year old male group, which would increase the estimated prevalence in the CVCR platform by approximately 1.7%. In contrast, missing data were not imputed in the studies by Zhao and Jia, and it is reasonable to assume that the true prevalence rate would be higher if missing values were imputed. Based on our projections, after imputing missing data using PSS, we predicted that the prevalence in 1998 and

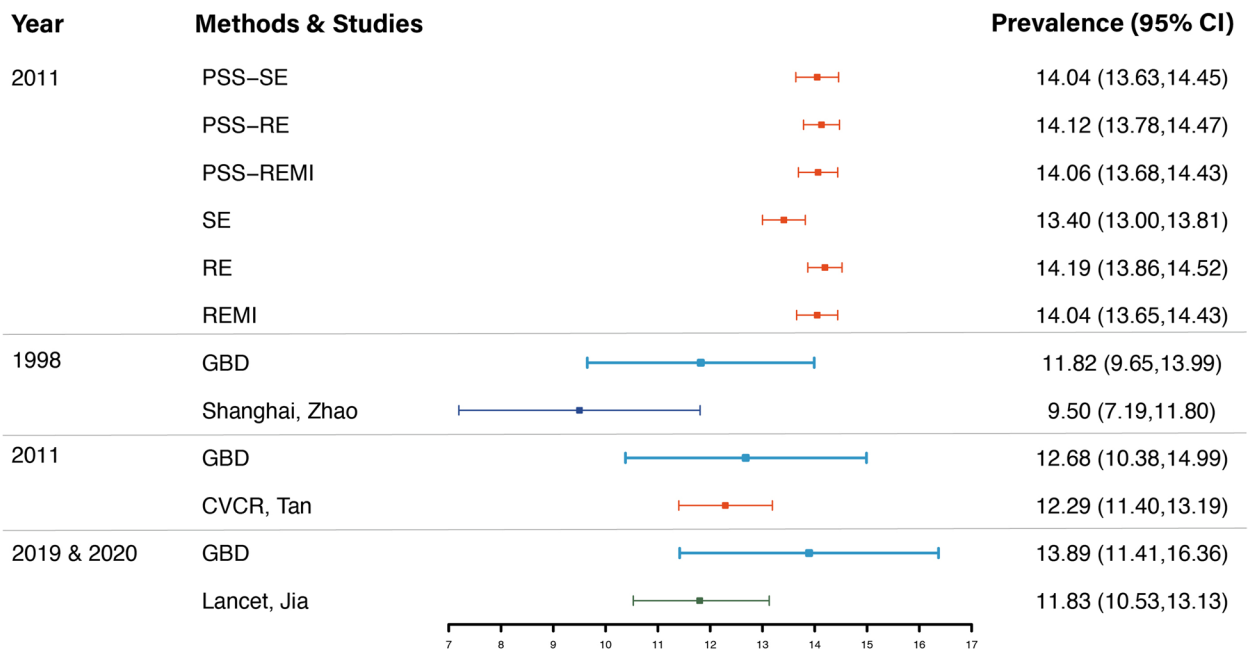

Fig. 4 Prevalence of dementia in CVCR and other studies in China by male group aged 80–89. Different colours represent different research years, dark blue for 1998, orange for 2011 and green for 2019. The results of the GBD study are shown in light blue and were considered as a reference in different years. The top two panels show the estimated results in CVCRwith and without PSS. Prevalence is expressed as the mean (95% CI). Prevalence in 2011 was estimated from the CVCR platform, and prevalence in 1998 and 2020 was estimated from published data by Zhao et al. and Jia et al., respectively. GBD data were obtained from the GHDx database

2020 would increase to about 11.2% and 13.5%, respectively, according to the Zhao and Jia studies.

Discussion

When we used different methods to estimate dementia diagnoses in patients who did not respond, the prevalence of dementia increased to 13.40–14.19% in the 80–89 age group. In a previous study [29], we compared the characteristics of responders and non-responders in phase II. It showed that non-responders in phase II were older, in poorer physical health, with lower cognitive performance, suggesting that non-responders were more likely to have dementia. Moreover, participants who screened positive for dementia in phase I had a higher rate of non-response. All this suggests that dementia and non-response in the dementia survey are closely related, and that MNAR is involved in the mechanism of missing dementia diagnosis [30]. Non-random non-response is a critical challenge for prevalence estimation in practice and can lead to biased results if not properly managed [31]. These may explain the underestimation of dementia prevalence when non-responders were ignored. When non-responders were ignored, the prevalence of dementia in male aged 80–89 years was lower in the CVCR than in the GBD (12.29% vs. 12.68%). After imputation for non-response, the prevalence of dementia in the CVCR was about 14%, suggesting that the true prevalence of dementia in this age group may be higher. Similarly, the prevalence of dementia in the population as a whole is likely to be higher than currently reported.

This study found that after using SE, RE and REMI to infer a diagnosis of dementia in non-responders, there were differences in prevalence in the population (11.64%, 12.33%, 11.98%). This is similar to the results of previous analyses based on the CVCR [17]. In previous studies, when the prevalence of dementia was estimated after imputing missing data using stratified weighting (SW), inverse probability weighting (IPW), hot-deck imputation (HDI) and ordinal logistic regression (OLR), the prevalence estimates ranged from 10 to 16% for dementia and showed greater variation. Some research has shown that by setting up a PS model, the association between missing propensity and dementia can be removed, thereby improving the performance of imputation models [32–35]. PSS would therefore be an ideal strategy. We recommend that this critical issue be addressed under the framework of the PSS: establish PS model and determine the missing mechanism, stratified veterans by the missing propensity score, then the same methods were used to estimate the prevalence of participants in each stratum, and finally the prevalence

was pooled. After these procedures, the consistency of the estimated prevalence of the different methods was improved (12.24%, 12.28%, 12.20%). MoCA and MMSE scores reflecting cognitive function were used to stratify the probability of non-response. Therefore, the cognitive level of patients in each stratum is more similar. At this point, the absence of diagnosis was weakly correlated with cognitive function itself in each stratum, and the missing mechanism was closer to MAR. In this way, consistency between different methods can theoretically be improved. The results of this study also suggest that controlling for MNAR may be more important than models that impute missing data [31].

Three methods can be used to estimate the prevalence of each stratum: SE, RE and REMI. SE is based on the expectation and variance of the observed proportion of people with dementia to impute missingness, which does not rely on covariates and is sensitive to MNAR. In RE, participants in each stratum have different characteristics, so we choose different covariates to build the logistic model, and the same covariate will have different estimated coefficients in different stratum. As a method of imputation rather than estimation, multiple imputation must be combined with estimation methods such as simple estimation or regression estimation [36]. The results of multiple imputation will generally have a larger variance, which is consistent with its aim of taking full account of the uncertainty in the data.

However, in the published literature on the prevalence of dementia in China, estimates of prevalence in the 80–89 age group are imprecise. Some studies included fewer people in the population, which is reflected in the large confidence interval for prevalence estimates in this age group [27, 28]; other studies used only historical data to estimate the current prevalence in the 80–89 age group [8, 13]. This phenomenon widely existed in the research among the oldest-old around the world [2]. Missing data are inevitable not only in observational studies [37] but also in clinical trials [38]. Older non-responders are more likely to have the disease being studied. Therefore, an optimal method for dealing with missing data is needed [39]. With the development of an ageing society, there will be an increasing number of older people who are more likely to have dementia and other chronic diseases. And research on the elderly will have larger sample sizes and more variables, resulting in a more complicated missing mechanism [19], as more causes can lead to missing data. Traditional data imputation methods are not suitable, and a joint model in statistics will be a new direction for dealing with missing data in future medical research.

The study found that the prevalence of dementia may be underestimated by 2%. An accurate estimate of dementia prevalence could help guide policy and health care resources. A study conducted to simulate resource use for dementia in Australia found that age-related health resource use increased as the dementia population grew. The study also found that the lack of provision of residential aged care could put a strain on hospital resources. In addition, a study reported that neurological disorders are among the leading causes of disability and death, highlighting the need for more cost-effective and rational resource allocation. Accurate prevalence estimates can help to effectively address the challenges posed by pension shortages and an ageing population.

The findings of this study should be interpreted alongside its limitations. First, for stratification, dividing the population equally by the quintiles of the propensity score is a simple and effective method but it is not the only one. In more extreme scenarios, for example if there are not enough responders in a particular stratum, we can reduce the number of strata with some loss of precision or make the stratum include more people. In the estimating overall prevalence, the weighted average method we use will remove the effect of differences in sample size between strata. Also, in the PS model, only some of the collected covariates were considered, while there are still some confounders that cannot be assessed. In addition, our study only used data from one platform to build this model, which may limit the generalizability of the methods. Therefore, external validation is needed in further research.

Conclusion

In conclusion, stratifying data according to the missing propensity and using appropriate prevalence estimation methods for each stratum can produce reliable estimates of the prevalence of dementia that are higher than the original estimates without accounting for missing data. Moreover, after PSS, the results of different estimation methods are more consistent.

Abbreviations

CVCR	Chinese Veteran Clinical Research
PSS	Propensity score stratification
PS	Propensity score
SE	Simple estimation
RE	Regression estimation
REMI	Regression estimation with multiple imputation
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
MCI	Mild cognitive impairment
MNAR	Missing not at random
MAR	Missing at random
MoCA	Montreal Cognitive Assessment
MMSE	Mini-Mental State Examination
PADL	Physical activities of daily living
IADL	Instrumental activities of daily living

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12874-023-01954-0.

Additional file 1.

Acknowledgements
We would like to thank all participants, caregivers and medical staffs of the Chinese Veteran Clinical Research (CVCR) Platform.

Authors' contributions
CS: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data; MYP: Drafting/revision of the manuscript for content, including medical writing for content; XXW: Drafting/revision of the manuscript for content, including medical writing for content; YMZ: Study concept or design; LNW: Study concept or design; Major role in the acquisition of data; JPT: Study concept or design; Major role in the acquisition of data KD: Study concept or design; Analysis or interpretation of data; NL: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data. All authors read and approved the final manuscript.

Funding
The part of analysis and interpretation of data and the work in writing the manuscript was funded by the National Natural Science Foundation of China (Project No. 81701067) and Beijing Natural Science Foundation (Project No. Z190021).
The CVCR platform, which included the design of the study and collection of data, were supported by the Special Research Project on Health Care, Health Sector of the General Logistics Department of People's Liberation Army (Project Number: 07BJZ04; 10BJZ19; 11BJZ09; 12BJZ46).

Availability of data and materials
All results presented in this study are objectively shown in this article and/or its Additional file. The R code of the study is available from corresponding authors Ke Deng and Nan Li. The datasets generated and/or analysed during the current study are not publicly available due to privacy or ethical restrictions but are available from corresponding author Jiping Tan on reasonable request.

Declarations

Ethics approval and consent to participate
All participants signed written informed consent. All data were anonymized. The design and protocol of the CVCR have been approved by the Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital(No. 20090820–02). The design and protocol of data analysis were approved by Ethics Committee of the Peking University Third Hospital (No. M2016114 and M2017055).

Consent for publication
Not applicable.

Competing interests
The authors have no conflicts of interest to declare.

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Received: 20 September 2022 Accepted: 16 May 2023
Published online: 27 May 2023

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Publisher's Note

· 流行病与统计方法 ·

东亚人群血压与心力衰竭的因果关联研究：两样本双向孟德尔随机化分析

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摘要：目的　利用两样本双向孟德尔随机化（MR）研究设计，探究东亚人群中三种血压指标与心力衰竭风险的关联。**方法**　从发表的全基因组关联研究（GWAS）中提取汇总数据进行分析，收缩压和舒张压的遗传工具变量来自韩国基因组与流行病学研究，脉压的遗传工具变量来自日本生物银行，心力衰竭的遗传工具变量来自一项包含五个日本队列的 GWAS 研究。采用单变量 MR、双向 MR 和多变量 MR 方法分析三种血压指标与心力衰竭风险的关联。**结果**　逆方差加权法显示收缩压（每升高 1 mm Hg，*OR* = 1.52；95% *CI*：1.25 ~ 1.84）、舒张压（1.62；1.34 ~ 1.95）和脉压（1.85；1.27 ~ 2.69）升高均可能增加患心力衰竭的风险，而心力衰竭对三种血压指标没有潜在的因果影响（$P > 0.05$）。多变量分析显示脉压经调整收缩压（1.25；0.77 ~ 2.05）或舒张压（1.46；0.95 ~ 2.23）后与心力衰竭风险没有显著关联。**结论**　在东亚人群中血压对心力衰竭可能存在单向的因果关联，脉压对心力衰竭风险不存在独立于收缩压和舒张压的直接效应。

关键词：血压；心力衰竭；孟德尔随机化；东亚

中图分类号：R541　　**文献标志码：**A　　**文章编号：**1003 - 8507(2023)10 - 1743 - 06

DOI：10.20043/j.cnki.MPM.202212037

Association between blood pressure and heart failure in East Asian population: a two-sample bidirectional Mendelian randomization study

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Abstract: Objective　To investigate the association between three blood pressure components and the risk of heart failure in the East Asian population by two-sample bidirectional Mendelian Randomization (MR) analysis. **Methods**　Summary data used in the study were extracted from published genome-wide association studies (GWASs). The instrumental variables were derived from the Korean Genome and Epidemiology Study for systolic and diastolic blood pressure, the BioBank Japan Project for pulse pressure, and a GWAS involving five Japanese cohorts for heart failure risk. Univariate MR, bidirectional MR, and multivariable MR were conducted to analyze the association between three blood pressure components and heart failure risk. **Results**　The results of the inverse variance weighted method demonstrated that systolic blood pressure (*OR* = 1.52 per 1 mm Hg increase; 95% *CI*: 1.25 - 1.84), diastolic blood pressure (1.62; 1.34 - 1.95), and pulse pressure (1.85; 1.27 - 2.69) were all associated with increased risk of heart failure, which however had no potential causal effect on the three blood pressure components ($P > 0.05$). Multivariable analysis showed no significant association between pulse pressure and heart failure risk after adjusting for systolic blood pressure (1.25; 0.77 - 2.05) or diastolic blood pressure (1.46; 0.95 - 2.23). **Conclusion**　Our findings suggest that there is a potential unidirectional causal association from blood pressure to heart failure in the East Asian population, and pulse pressure has no direct effect on heart failure risk when taking systolic or diastolic blood pressure into account.

Keywords: Blood pressure; Heart failure; Mendelian randomization analysis; East Asia

心力衰竭（heart failure, HF）是由心脏结构或功能异常引起的一种临床综合征，在我国患病率呈上升趋势[1]。高血压已成为过早死亡的首要原因[2]，临床上主要使用收缩压（systolic blood pressure, SBP）和舒张压（diastolic blood pressure, DBP）进行衡量，此外脉压（pulse pressure, PP）也是预测心血管风险的重要

基金项目：国家重点研发计划（2019YFC2003401）；国家自然科学基金（82173499）

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指标。目前上述三种血压指标与 HF 风险的关联证据主要来自西方人群,且缺乏探究 PP 与 HF 之间双向因果关系的研究[3-4]。

由于等位基因在亲代遗传给子代时随机分配,孟德尔随机化(Mendelian randomization, MR)研究可以利用遗传变异作为工具变量进行"天然的随机对照研究",对可改变危险因素与疾病结局的关联进行因果估计[5],其中两样本设计使用来自同一人群两个样本的遗传数据开展分析。在传统 MR 设计的基础上,一些新的范式被提出以解决不同问题,如双向 MR 可用来估计结局对暴露产生的因果作用,而多变量 MR 可用来估计多个相关的暴露表型对结局的独立因果效应[6]。近年来一些基于东亚国家的大规模全基因组关联研究(genome-wide association study, GWAS)的发表为适用于东方人群的因果证据的产生提供了新的机会[7-9]。

本研究旨在利用最新的东亚人群 GWAS 汇总数据进行两样本双向 MR 分析,探究三种血压指标与 HF 风险的双向因果关系。

1 方 法

1.1 研究设计 本研究的暴露为 SBP、DBP 和 PP,结局为是否患有 HF。MR 研究的工具变量一般是单核苷酸多态性位点(single nucleotide polymorphisms, SNP)。SBP 和 DBP 的 SNP 信息提取自韩国基因组与流行病学研究(Korean Genome and Epidemiology Study, KoGES)的 GWAS[7],PP 的 SNP 信息提取自日本生物银行队列(BioBank Japan Project, BBJ)的 GWAS[8]。结局的 SNP 信息提取自整合了五个日本队列的 GWAS[9]。上述研究的信息见表 1。

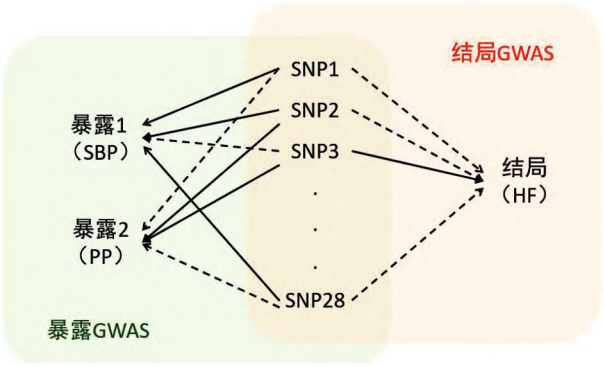
表 1 本研究使用的 GWAS 汇总数据

Table 1 Summary of the GWASs included in this study

变量	样本量	人群	年份	调整变量
SBP	72 265 人	韩国的 KoGES	2022	年龄、性别、前 10 个主成分、相关测量信息
DBP	72 265 人	韩国的 KoGES	2022	年龄、性别、前 10 个主成分、相关测量信息
PP	145 445 人	日本的 BBJ	2021	年龄、年龄的平方、性别、年龄乘性别项、年龄的平方乘性别项、前 20 个主成分
HF	212 453 人(病例 9 413,对照 203 040)	日本的 BBJ、ToMMo、IMM、Japan Public Health Center-based Prospective Study 和 Japan Multi-institutional Collaborative Cohort Study	2020	年龄、性别、前 5 个主成分

1.2 工具变量选择 单变量 MR 分析从各暴露的汇总数据中选取最小等位基因频率 >1% 的常见 SNP,保留在全基因组水平显著的位点($P \leqslant 5 \times 10^{-8}$),参考千人基因组计划东亚人群进行连锁不平衡聚集,参数设置 $r^2 < 0.1$,距离阈值为 10 000 千碱基对(kb)。进一步剔除无法与结局 GWAS 里相应 SNP 信息协调的位点,使用 MR Steiger filtering[10] 剔除与结局的相关性大于暴露的位点。双向 MR 分析首先从结局的汇总数据中选取与 HF 显著相关的 SNP,经连锁不平衡聚集后从暴露的汇总数据中提取相应位点信息,参数设置同单变量 MR 分析。多变量 MR 分析允许遗传变异对放入模型中的多个暴露有多效性效应,由于三种血压指标高度相关(PP = SBP - DBP),所以将其两两一组纳入模型。多变量 MR 不要求工具变量与所有暴露都相关,只需选取与模型中任一种血压指标显著相关的 SNP,将它们合并后进行聚集,然后从结局 GWAS 中提取相应位点的汇总信息。见图 1。

1.3 统计学分析 可靠的 MR 分析建立在三个前提假设下:(1)相关性假设(工具变量与血压密切相关),(2)独立性假设(工具变量不能与混杂因素相关),(3)排他限制假设(工具变量只能通过血压影响 HF)[5]。为测试相关性假设,计算工具变量能够解释的暴露变



注:以纳入 SBP 和 PP 的多变量 MR 分析为例,实线表示遗传位点与性状显著相关($P \leqslant 5 \times 10^{-8}$),虚线表示遗传位点与性状无显著相关关系。

图 1 多变量孟德尔随机化示意图

Fig. 1 Schematic of themultivariable MR design

异的比例 R^2 和 F 统计量,若 $F > 10$ 则说明违反该假设从而引入弱工具变量偏倚的可能性很小。其他两个假设无法直接验证,但可用敏感性分析和一些检验方法进行评估。

单变量 MR 分析主要使用逆方差加权法(inverse variance weighted, IVW)计算比值比(odds ratio, *OR*)

和 95% 置信区间(confidence interval, *CI*),该方法假设所有 SNP 均为有效工具变量且平均水平多效性为零,因此我们还进行了一系列敏感性分析,包括可以在无效工具变量存在的情况下进行稳健估计的加权中位数法和加权众数法、可以在水平多效性存在的情况下进行稳健估计的 MR - Egger 回归和可以鉴定并剔除异质性 SNP 的 MR - PRESSO (Pleiotropy RESidual Sum and Outlier)[6]。双向 MR 分析只识别出了单个 SNP,因此采用 Wald 比值法进行估计,将 SNP 与结局的关联系数除以 SNP 与暴露的关联系数[11]。多变量 MR 分析使用多变量 IVW 作为主分析,并额外进行多变量 MR - Egger 和 LASSO(Least Absolute Shrinkage and Selection Operator)分析,后者可以对无效工具变量进行惩罚,仅使用鉴定有效的工具变量进行计算。此外,由于 SBP 和 DBP 的工具变量来自同一人群,使用 PhenoSpD[12] 估计两者的表型相关性,以对多变量 MR 的结果进行调整[13]。

工具变量之间的异质性使用 IVW 的 Cochran *Q* 和 MR - Egger 的 Rücker *Q* 检验,方向水平多效性使用 MR - Egger 的截距项进行测量,以 0.05 为显著 *P* 值阈值。所有分析在 4.2.1 版本的 R 语言中进行,采用双侧检验。由于暴露因素有三个,除特殊说明外,以 Bonferroni 校正后 $P < 0.017$ 代表存在统计学意义差异。

2　结　果

2.1　单变量孟德尔随机化　三组遗传工具均通过了 MR Steiger 检验,R^2 分别为 1.56%、1.49% 和 0.59%,*F* 统计量分别为 160.4、146.1 和 70.4,表示 MR 结果不太可能受弱工具变量偏倚的影响。IVW 方法显示遗传预测的 SBP、DBP 和 PP 每增加 1 mm Hg,HF 的风险分别显著增加 52%(*OR* = 1.52; 95% *CI*: 1.25 ~ 1.84)、62%(*OR* = 1.62; 95% *CI*: 1.34 ~ 1.95)和 85%(*OR* = 1.85; 95% *CI*: 1.27 ~ 2.69),见表 2。MR - Egger、加权中位数法、加权众数法和 MR - PRESSO 给出了一致的估计,其回归斜率见图 2。*Q* 检验没有观察到 SNP 之间存在显著异质性($P > 0.05$);MR - Egger 截距项与零没有显著差异($P > 0.05$),漏斗图中点的分布大致对称,表明不存在未平衡的方向水平多效性。见表 2、图 2。

表 2　血压与心力衰竭的单变量孟德尔随机化分析结果

Table 2　Univariate MR estimates of blood pressure traits and heart failure

暴露	方法	SNP	*OR* (95% *CI*)	*P* 值	$P_{Q检验}$	$P_{截距}$
SBP	IVW	21	1.52 (1.25 ~ 1.84)	< 0.001	0.247	
	MR - Egger	21	2.09 (1.15 ~ 3.82)	0.026	0.261	0.284
	加权中位数	21	1.56 (1.20 ~ 2.03)	< 0.001		
	加权众数	21	1.63 (1.18 ~ 2.25)	0.005		
	MR - PRESSO	21	1.52 (1.25 ~ 1.84)	< 0.001		
DBP	IVW	22	1.62 (1.34 ~ 1.95)	< 0.001	0.346	
	MR - Egger	22	1.74 (0.95 ~ 3.17)	0.089	0.294	0.812
	加权中位数	22	1.55 (1.19 ~ 2.02)	< 0.001		
	加权众数	22	1.56 (1.10 ~ 2.19)	0.015		
	MR - PRESSO	22	1.62 (1.34 ~ 1.95)	< 0.001		
PP	IVW	18	1.85 (1.27 ~ 2.69)	0.001	0.089	
	MR - Egger	18	1.50 (0.17 ~ 13.43)	0.720	0.066	0.852
	加权中位数	18	1.41 (0.90 ~ 2.23)	0.129		
	加权众数	18	1.57 (0.79 ~ 3.13)	0.206		
	MR - PRESSO	18	1.85 (1.27 ~ 2.69)	0.005		

2.2　双向孟德尔随机化　Wald 比值法没有发现 HF 可能对 SBP($\beta = 0.020$; $P = 0.734$)、DBP($\beta = 0.006$; $P = 0.917$)或 PP($\beta = 0.015$; $P = 0.699$)产生因果效应的证据。

2.3　多变量孟德尔随机化　遗传工具的条件 *F* 统计量均大于 10。多变量 IVW 的结果表明遗传决定的 SBP($P = 0.015$)和 DBP($P = 0.010$)对 HF 风险存在独立于 PP 的直接效应,而 PP 与 HF 的关联在调整 SBP($P = 0.375$)或 DBP($P = 0.092$)后消失,未观察到 SBP($P = 0.667$)和 DBP($P = 0.167$)独立于彼此的直接效应。见表 3。多变量 MR - Egger 和 LASSO 的估计与主分析相似。*Q* 检验和 MR - Egger 没有检出异质性和方向水平多效性的存在。

3　讨　论

本研究利用来自东亚的 GWAS 汇总数据开展两样本双向 MR 研究,对 SBP、DBP 和 PP 三种血压成分与 HF 风险的关系进行因果估计。研究显示在东亚人群中,遗传预测的三种血压指标每降低1 mm Hg可以大幅度降低 HF 风险,且 HF 不太可能反向影响血

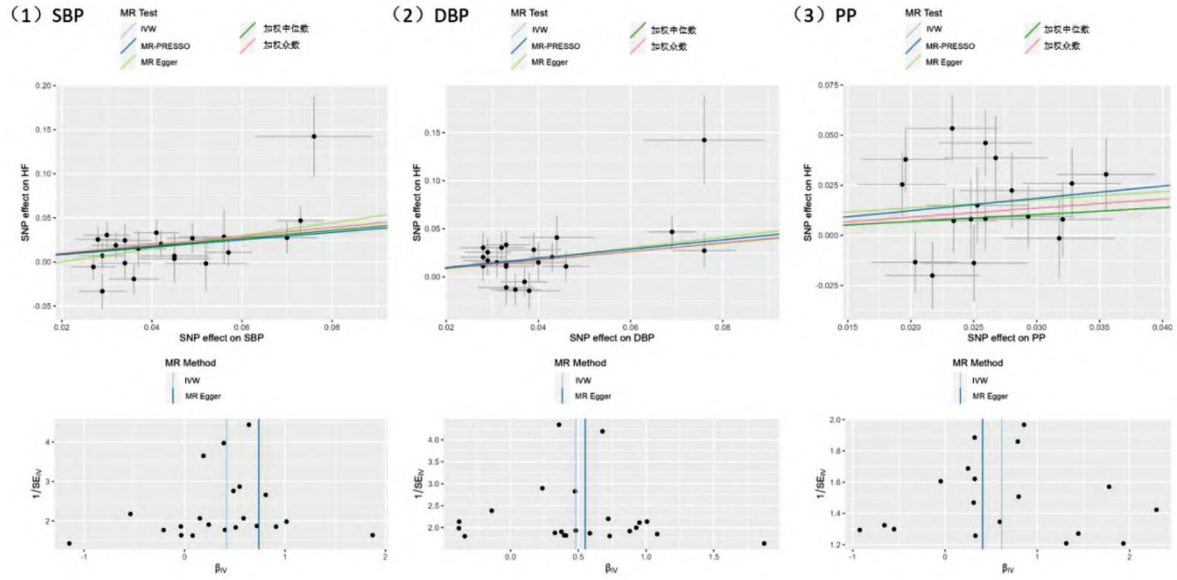


图 2　单样本孟德尔随机化分析的散点图和漏斗图

Fig. 2　Scatter plots and funnel plots of univariate MR analyses

表 3　血压与心力衰竭的多变量孟德尔随机化分析结果

Table 3　Multivariable MR estimates of blood pressure traits and heart failure

暴露 1	暴露 2	方法	SNP	*OR*(95% *CI*)	*P* 值	$P_{Q检验}$	$P_{截距}$
SBP	DBP	IVW	26	0.82(0.33 ~ 2.02)	0.667	0.381	
		Egger	26	0.85(0.34 ~ 2.12)	0.725	0.379	0.468
		Lasso	24	0.88(0.36 ~ 2.14)	0.782		
	PP	IVW	28	1.50(1.11 ~ 2.03)	0.015	0.174	
		Egger	28	1.49(1.00 ~ 2.22)	0.051	0.157	0.951
		Lasso	26	1.40(1.06 ~ 1.85)	0.018		
DBP	SBP	IVW	26	1.99(0.77 ~ 5.12)	0.167	0.381	
		Egger	26	2.32(0.82 ~ 6.55)	0.113	0.379	0.468
		Lasso	26	1.85(0.73 ~ 4.67)	0.194		
	PP	IVW	30	1.48(1.12 ~ 1.96)	0.010	0.084	
		Egger	30	1.76(1.03 ~ 3.03)	0.039	0.083	0.458
		Lasso	30	1.48(1.12 ~ 1.96)	0.006		
PP	SBP	IVW	28	1.25(0.77 ~ 2.05)	0.375	0.174	
		Egger	28	1.24(0.63 ~ 2.42)	0.538	0.157	0.951
		Lasso	26	1.23(0.79 ~ 1.94)	0.362		
	DBP	IVW	30	1.46(0.95 ~ 2.23)	0.092	0.084	
		Egger	30	1.40(0.90 ~ 2.18)	0.135	0.083	0.458
		Lasso	30	1.46(0.95 ~ 2.23)	0.081		

压。此外,SBP 和 DBP 对 HF 的因果作用在调整 PP 后仍然存在,而 PP 与 HF 的关联在多变量分析中未达到显著水平。

高血压与 HF 的关系已被多项研究证实,然而本研究在东亚人群中得到的关联大小明显高于来自西方人群的结果。一项欧洲研究显示,SBP 每升高 10 mm Hg,HF 发生风险增加 26%(*OR* = 1.23; 95% *CI*: 1.13 ~ 1.40);DBP 每升高 5 mm Hg,HF 发生风险增加 24%(*OR* = 1.24; 95% *CI*: 1.13 ~ 1.35)[14]。而在本研究中每 1 mm Hg 的 SBP 上升与 HF 风险增加 52%有关,每 1 mm Hg 的 DBP 上升与 HF 风险增加 65%有关。这种东西方的差异也出现在以往的随机对照试验中。一项在北美开展的试验发现,相比于以 SBP < 140 mm Hg 为目标的标准治疗,以 SBP < 120 mm Hg为目标的强化治疗可以进一步降低 HF 风险,风险比为 0.77(95% *CI*: 0.62 ~ 0.95)[15]。一项在中国开展的试验发现 110 ~ 130 mm Hg 的 SBP 治疗目标相比 130 ~ 150 mm Hg 可以更大的降低失代偿性 HF 的发生率,风险比为 0.27(95% *CI*: 0.08 ~ 0.98)[16]。这种差异可能是由于东亚人群的血压均值普遍低于西方人群且变异度更小,如韩国 KoGES 队列的 SBP 为(均值 ± 标准差,122.6 ± 15.4)

mm Hg[7],英国 UK Biobank 队列的 SBP 为(138.0 ± 19.3) mm Hg。暴露变异度小,GWAS 中回归得到的 SNP 与暴露的关联系数就会小,对于 MR 计算公式来说,位于分母的 SNP 与暴露的关联越小,越可能得到较大的估计值[11]。

有研究对血压升高引起 HF 的机制进行了探讨[17]。慢性血压高和全身性外周阻力增加会引起血流机械应力增加和冠状动脉内皮炎症反应,左心室心肌细胞发生纤维化和肥大,导致左心室舒张功能障碍,心脏发生代偿性变化,加快左室肥厚等心脏重构进程,最终临床表现为心衰。本研究的双向 MR 分析未观察到遗传预测的 HF 与血压的关联,类似地,基于欧洲人群的一项遗传学研究未发现心肌梗死对血压的因果作用[18]。这提示患有 HF 不会引起血压水平的长期变化,临床中部分 HF 患者出现的致命性血压下降可能是病情进展过程中其他危险因素的作用结果,试验发现通过心脏同步化治疗可以提升血压从而改善 HF 预后[19]。

在东亚人群 HF 的发病过程中,PP 可能不是一个有因果关系的独立危险因素。美国弗雷明汉心脏研究在 SBP≥140 mm Hg 的参与者中报道了 PP 与 HF 风险的显著关联,认为 PP 和 SBP 相比 DBP 指标更能够代表 HF 风险[4]。另一项美国队列研究在控制 SBP 或 DBP 后,发现 PP 仍与 HF 显著相关[20]。我们的研究表明这种关联可能不具有真正的因果效应,PP 有关的观察性研究结果可能受到残余混杂或与其他血压指标强相关关系的影响。此外,我们未在东亚人群中发现 SBP 独立于 DBP 的直接效应。此前一项基于亚太地区的队列研究显示在 DBP 的模型中增加 SBP 会明显提高对中风和冠状动脉疾病的风险捕捉能力,但在 SBP 的模型中增加 DBP 不会提高拟合优度[21]。西方人群的研究显示遗传预测的 SBP 与 HF 的关联在控制 DBP 后仍然存在,而遗传预测的 DBP 与 HF 的关联在控制 SBP 后大幅缩减为零[3]。因此本研究 SBP 与 DBP 的多变量结果需要在基于更大样本量 GWAS 的研究中进行验证。

本研究优势在于遗传数据全部来源于东亚人群,可以弥补有关亚洲人血压与 HF 关联证据的缺失。此外,我们使用了 MR 研究框架进行因果推断,由于遗传信息在时间顺序上先于出生后环境因素的暴露,因此这种方法可以避免观察性研究中常见的由混杂因素和反向因果带来的偏倚,而且相比于随机对照试验面临的实施成本和伦理问题,MR 研究可以更高效地进行关联的无偏估计[5]。然而我们的研究也存在一些局限性。首先,提供结局和 PP 工具变量的 GWAS 研究都包含 BBJ 的参与者,因此在样本上有部分重叠,使与 PP 有关的结果远离无效假设。此外,由于东亚人群 GWAS 样本量小于西方人群,识别出的显著 SNP 数量较少,置信区间较大,因此未来需要在更大亚洲人群中进行 GWAS 研究或对多个亚洲人群遗传研究结果进行荟萃分析。

综上所述,本研究利用遗传数据进行两样本双向 MR 分析,发现东亚人群 SBP、DBP 和 PP 对 HF 风险存在单向的因果影响,且效应量大于西方人群,提示同等的降压水平可能在亚洲人群中产生更大的健康收益。在这三种血压指标中,PP 没有显示出对 HF 风险的直接因果效应,因此 PP 不太可能是 HF 的独立预测指标。

志谢　感谢所有为本研究的开展提供宝贵数据的全基因组关联研究

利益冲突声明　本研究不存在任何利益冲突

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收稿日期:2022-12-10

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收稿日期:2022-12-05