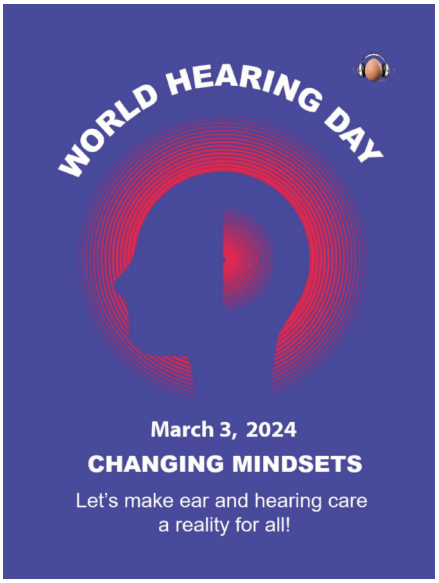
ISSN 2096-7071 (Print)
ISSN 2096-3101 (Online)
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 6 No. 9 Mar. 1, 2024

CDC weekly

中国疾病预防控制中心周报



Preplanned Studies

Combined Effect of Outdoor Time and Other Modifiable Factors on Myopia Incidence Among Children and Adolescents — 9 PLADs, China, 2020 151

Analysis of Hot Topics Regarding Global Smart Elderly Care Research — 1997–2021 157

Inflection Point Age in the Middle and Older Women — Jiangxi Province, China, 2020–2022 162

Methods and Applications

Genetic Insights into Glycine's Protective Role Against CAD — European and East Asia, 2015 and 2020 168

ISSN 2096-7071
09
9 772096 707248

China CDC Weekly

Cover Image: adapted from the World Health Organization, https://www.who.int/campaigns/world-hearing-day/2024.

Preplanned Studies

Combined Effect of Outdoor Time and Other Modifiable Factors on Myopia Incidence Among Children and Adolescents — 9 PLADs, China, 2020

Panliang Zhong[1]; Yunfei Liu[1]; Ning Ma[1]; Jiajia Dang[1]; Di Shi[1]; Shan Cai[1]; Ziyue Chen[1]; Yanhui Dong[1]; Peijin Hu[1]; Jun Ma[1]; Patrick W.C Lau[2]; Randall S. Stafford[3]; Yi Song[1,#]

Summary

What is already known about this topic?

Myopia has been identified as a significant emerging challenge and policy priority among children and adolescents in China by the Ministry of Education and seven other departments. Limited research has been conducted to investigate the collective impact of outdoor time and other modifiable factors on the incidence of myopia.

What is added by this report?

This study provides support for the protective effect of combining increased outdoor time with other prevention strategies in reducing the incidence of myopia. The results indicate the presence of a dose-response relationship.

What are the implications for public health practice?

To effectively prevent myopia, it is important to implement comprehensive interventions that encompass various aspects such as outdoor time, eye-use habits, eye-use environments, and lifestyle modifications.

Myopia is a global public health concern, affecting approximately 30% of the world's population and is expected to reach 50% by 2050 (*1*). In China, myopia was recognized as a significant health issue by the Lancet Commission in 2021 and identified as a major emerging challenge and policy priority for children and adolescents by the Ministry of Education and seven other departments of the People's Republic of China (*2*–*3*). Increasing outdoor time has been identified as a preventive measure against myopia in children (*4*). However, other modifiable factors, with equivocal to modest evidence of a relationship with myopia, which have not been studied in depth, are worth investigation, given a looming myopia epidemic (*5*). In this study, researchers analyzed follow-up data to examine the combined impact of outdoor time and other modifiable factors on myopia incidence. Its findings revealed a dose-response relationship between these factors and myopia risk. To effectively combat myopia, comprehensive interventions addressing multiple factors are necessary.

Data were collected from a follow-up investigation conducted in China across nine provincial-level administrative divisions (PLADs): namely Guangxi, Chongqing, Gansu, Hunan, Henan, Shanxi, Fujian, Shanghai, and Jiangsu. The investigation took place between September and November of 2020, with baseline information gathered in June of the same year. Supplementary Figure S1 (available at https://weekly.chinacdc.cn/) provides an overview of the sampling and investigation procedures, which have been previously published (*6*). A total of 3,993 children and adolescents in grades 1–6, 7–8, and 10–11 who did not have myopia at baseline were included in the analysis. Students with missing information regarding their parents' myopia status, outdoor time, and more than three other modifiable factors were excluded (Supplementary Figure S2, available at https://weekly.chinacdc.cn/). In this population-based study, myopia was defined as low unaided distance visual acuity (<5.0) and non-cycloplegic spherical equivalent refractive error (spherical equivalent <–0.50 Diopter). Questionnaires were used to measure outdoor time and ten other modifiable factors, including eye-use habits (eye exercises, screen time, lying down while watching/reading, watching a screen in darkness, posture reminding), eye-use environment (desktop brightness on sunny days, light brightness in the evening, seat/desk fitted for height), and lifestyle (sleep duration, sedentary time). Outdoor time and the other modifiable factors were categorized as binary variables (assigned 0 or 1 point according to Table 1). The ten other modifiable factors were then summed up to

TABLE 1. Assignment of modifiable factors.

Variables	Question	Assignment	
		0	1
Outdoor time	What was your daily exposure to sunlight? (Time spent in direct sunlight)	<2 h	≥2 h
Eye-use habits			
Eye exercises	On average, how many times a day do you do eye exercises during school days this semester?	<2 times/day	≥2 times/day
Screen time	In the past 7 days, how much time did you spend watching TV, using computer, mobile phone and tablet every day (including surfing the Internet, watching movies, browsing the web, and playing games)?	≥2 h	<2 h
Lying down while watching/reading	In the past 7 days, have you read a book or watched a video (tablet or phone) lying down?	Often	Occasionally/never
Watching a screen in darkness	In the past 7 days, have you continued to look at your phone or tablet after turning off the lights?	Often	Occasionally/never
Posture reminding	In the past 7 days, have your parents or teachers reminded of your reading and writing posture?	Occasionally/never	Often
Eye-use environment			
Desktop brightness on sunny days	Is your desktop bright enough on a sunny day?	Not very bright	Very bright
Light brightness in the evening	Do you think the lights are bright enough when you study at night?	Not bright enough	Bright enough
Seat/desk fitted for height	Do you think your desk and seat are fitted for your height?	No	Yes
Lifestyle			
Sleeping duration	In the past 7 days, how long did you sleep on average per day?	< 9 h or >11 h for the grade 1–6 children <8 h or >10 h for the grade 7–11 children	≥9 h and ≤11 h for the grade 1–6 children ≥8 h and ≤10 h for the grade 7–11 children
Sedentary time	In the past 7 days, how long have you been sitting on average per school day?	≥5 h	<5 h

create a cumulative effect score (CES) ranging from 0 to 10, using multiple imputations to account for missing information. We performed several regressions according to different cutoff points of CES, assigning the combined effect of outdoor time and modifiable factors based on cutoff points of CES and outdoor time. For example, if the cutoff point was defined as 4, the CES was transformed into a binary variable called "binary cumulative effect score (BCES)," with 1 point for CES≥4 and 0 points for CES<4. Regression analysis was performed six times with cutoff points from 3 to 8. A cutoff point of 3 tested those with CES<3 to those with CES≥3. The more extreme cutoff points (1, 2, 9, and 10) did not provide meaningful information due to the creation of very small comparison groups. A binomial generalized linear mixed model with a log link function was employed to explore the combined effect of outdoor time and modifiable factors on the incidence of myopia. The combined effect was defined as a binary variable, that was "positive" when outdoor time was ≥2 hours daily and BCES was 1 point, and was "negative" when outdoor time was <2 hours daily or BCES was 0 points (Supplementary Figure S3, available at https://weekly.chinacdc.cn/). The regression model adjusted for sex, residence (urban or rural), grade, parents' myopia status (0 or 1 or 2 parents with myopia), and the cluster effect of the PLAD. The same analyses were conducted for the three categories of modifiable factors. All statistical analyses were performed using R (version 4.2.2; R Core Team, 2022, R Foundation for Statistical Computing, Vienna, Austria), with the mice package (version 3.16.0) used for multiple imputation and the lme4 package (version 1.1.34) used for the regression analyses.

No individual modifiable factor, including outdoor time, showed a significant association with incident myopia (Table 2, all P>0.05). However, there was a dose-response relationship between the combined effect and outdoor time with respect to myopia risk. As the number of modifiable factors increased, the prevalence ratio (PR) decreased. Furthermore, in the total sample, a statistically significant association between the combined effect and myopia was observed when the combined effect score (CES) reached 7 [PR=0.81, 95% confidence interval (*CI*), 0.67, 0.98].

TABLE 2. Effect of single modifiable factors on myopia incidence.

Variables	Total		1–6 grades		7–11 grades	
	PR (95% *CI*)	*P*	PR (95% *CI*)	*P*	PR (95% *CI*)	*P*
Outdoor time						
0	Ref		Ref		Ref	
1	0.92 (0.78, 1.08)	0.315	0.93 (0.77, 1.12)	0.434	0.90 (0.64, 1.26)	0.530
Eye exercises						
0	Ref		Ref		Ref	
1	0.96 (0.80, 1.14)	0.611	1.00 (0.81, 1.22)	0.974	0.82 (0.57, 1.17)	0.272
Screen time						
0	Ref		Ref		Ref	
1	1.04 (0.84, 1.30)	0.697	0.92 (0.69, 1.23)	0.586	1.19 (0.86, 1.66)	0.297
Lying down watching/reading						
0	Ref		Ref		Ref	
1	0.96 (0.71, 1.30)	0.785	0.76 (0.50, 1.16)	0.205	1.17 (0.76, 1.80)	0.474
Watching screen in darkness						
0	Ref		Ref		Ref	
1	0.98 (0.66, 1.45)	0.911	0.69 (0.37, 1.29)	0.244	1.14 (0.69, 1.87)	0.607
Posture reminding						
0	Ref		Ref		Ref	
1	0.98 (0.83, 1.16)	0.845	0.95 (0.79, 1.14)	0.578	1.11 (0.78, 1.59)	0.558
Desktop brightness in sunny day						
0	Ref		Ref		Ref	
1	0.86 (0.73, 1.01)	0.070	0.91 (0.75, 1.11)	0.359	0.74 (0.55, 1.00)	0.050
Light brightness in the evening						
0	Ref		Ref		Ref	
1	1.15 (0.78, 1.70)	0.484	1.49 (0.85, 2.63)	0.164	0.79 (0.46, 1.34)	0.380
Seat/desk fitted for height						
0	Ref		Ref		Ref	
1	0.82 (0.65, 1.03)	0.092	0.89 (0.65, 1.22)	0.477	0.70 (0.49, 0.99)	0.044
Sleeping duration						
0	Ref		Ref		Ref	
1	0.90 (0.76, 1.07)	0.229	0.89 (0.74, 1.08)	0.227	0.94 (0.64, 1.38)	0.475
Sedentary time						
0	Ref		Ref		Ref	
1	0.93 (0.79, 1.10)	0.403	0.95 (0.79, 1.14)	0.579	0.87 (0.60, 1.26)	0.748

Note: The model adjusted sex, residence (urban or rural), grade, parents' myopia status (0 or 1 or 2 parents with myopia), and the cluster effect of the PLAD.
Abbreviation: PR=prevalence ratio; *CI*=confidence interval; PLAD=provincial-level administrative division.

Similar results were found in children in grades 1–6; the statistically significant association appeared when the CES reached 8 (PR=0.76, 95% *CI*: 0.60, 0.97), and a dose-response relationship existed. However, no statistically significant associations or dose-response relationships were observed in children in grades 7–11 (Figure 1A).

In terms of eye-use habits, a statistically significant association between the combined effect of outdoor time and eye-use habits on myopia was observed when the CES subset (ranging from 0 to 5) reached a score of 5 points. This association was found in both the total sample (PR=0.60, 95% *CI*: 0.40, 0.89) and grade 1–6 children (PR=0.63, 95% *CI*: 0.42, 0.94), but not

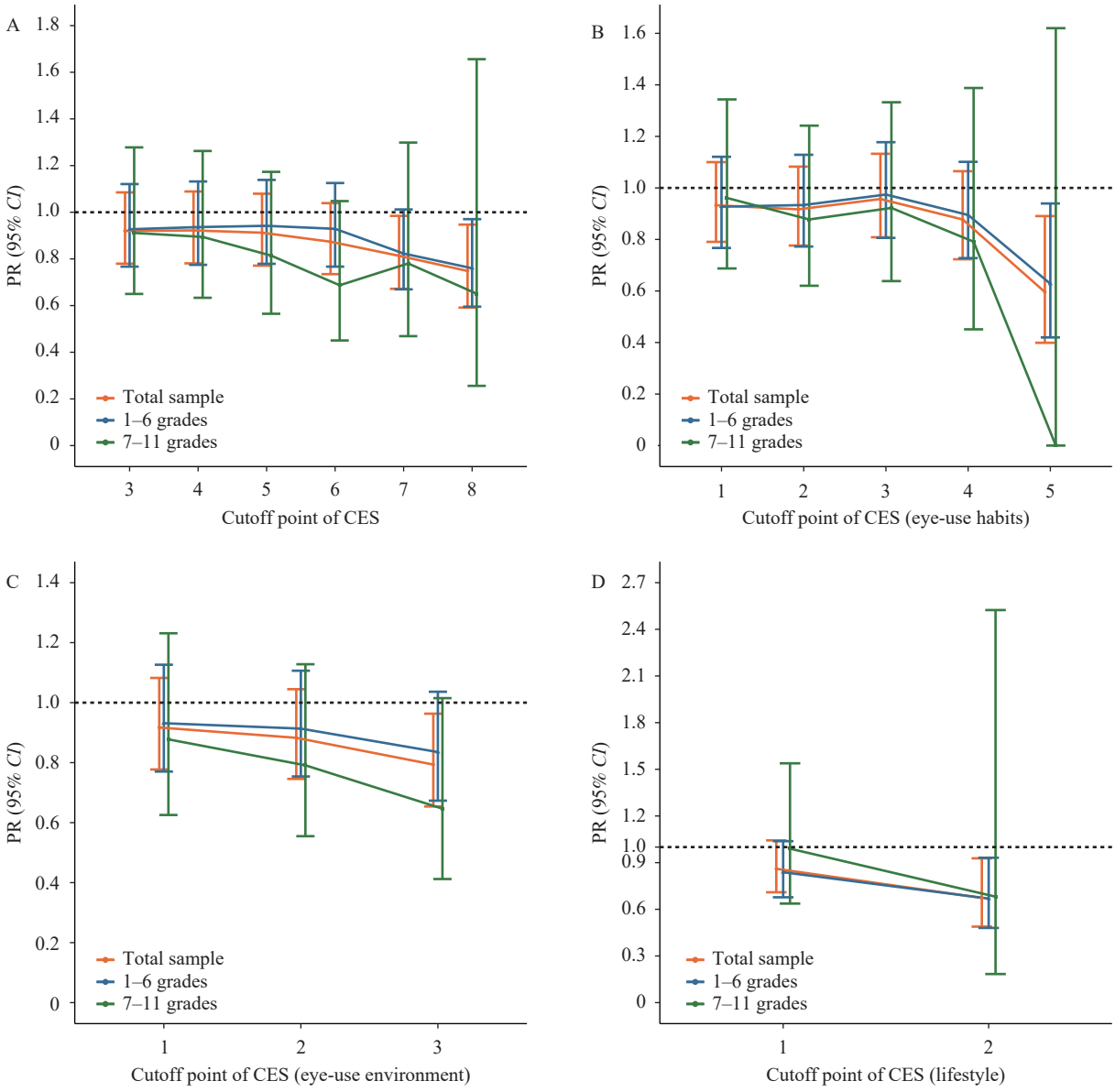


FIGURE 1. The combined effect of outdoor time and other modifiable factors on myopia incidence. (A) The combined effect of outdoor time and ten modifiable factors on myopia incidence; (B) the combined effect of outdoor time and five modifiable factors of eye-use habits on myopia incidence; (C) the combined effect of outdoor time and three modifiable factors of eye-use environment on myopia incidence; (D) the combined effect of outdoor time and two modifiable factors of lifestyle on myopia incidence.

Note: We conducted a binomial generalized linear mixed model with the log link function in every cutoff point of CES, respectively, and every model had a PR of the combined effect of outdoor time and modifiable factors on myopia incidence. The model adjusted sex, residence (urban or rural), grade, parents' myopia status (0 or 1 or 2 parents with myopia), and the cluster effect of the PLAD.

Abbreviation: CES=cumulative effect score; PR=prevalence ratio; *CI*=confidence interval; PLAD=provincial-level administrative division.

in grades 7–11. Regarding the eye-use environment, a statistically significant association was found when the CES subset (ranging from 0 to 4) reached a score of 3 points. However, this association was only observed in the total sample (PR=0.79, 95% *CI*: 0.65, 0.96). For lifestyle factors, a statistically significant association was present when the CES subset (ranging from 0 to 2) reached a score of 1 point. This association was found in both the total sample (PR=0.67, 95% *CI*: 0.49, 0.93) and grade 1–6 children (PR=0.67, 95% *CI*: 0.48, 0.93) (Figure 1B–D).

DISCUSSION

Although no significant individual modifiable factors were found to be associated with myopia, there was a statistically significant combined effect of outdoor time and modifiable factors on the incidence of myopia when the CES reached seven points. This finding supports conclusions about the protective effects of the combination of outdoor time and modifiable factors in preventing myopia. It also confirms that modifiable factors, which have insufficient evidence of a direct association with myopia, do have a protective effect against myopia. These effects may be obscured by their weak individual influences, but when they are cumulated and combined with outdoor time, their protective effects become apparent and can contribute to reversing the myopia epidemic (*6*). These findings align with the 2018 national plan launched by the Ministry of Education and seven other departments of the People's Republic of China, which emphasized the need for comprehensive interventions to protect children from myopia (*3*). Rather than focusing solely on factors with the highest level of evidence, the government should address modifiable factors that have the potential to harm the public. Ignoring these factors could delay the implementation of beneficial policies and perpetuate preventable burdens (*7*).

A similar pattern was observed in children from grades 1–6 but not in children from grades 7–11, potentially due to the weakening effect of educational pressure (*8*–*9*). In China, children from grades 7–9 face the pressure of the national high school entrance exam, while children from grades 10–12 face the pressure of the national college entrance exam. This highlights the need for differentiated recommendations for myopia prevention, taking into account the specific challenges faced by middle school students compared to primary school students.

In this study, researchers aimed to examine the combined effects of outdoor time and various modifiable factors on myopia. The study's findings demonstrate that the combination of modifiable factors and outdoor time significantly influences myopia when an adequate CES is achieved. These modifiable factors encompass three categories: eye-use habits, lifestyle, and eye-use environments. Effective interventions for all these categories should be implemented at multiple levels, including individuals, families, and schools. While the proactive engagement of children is crucial in shaping eye-use habits and lifestyles, the support and guidance from families and schools should not be underestimated. Moreover, creating a vision-friendly environment in schools and at home, such as ensuring bright lighting and appropriately fitted seats and desks, is essential. Children themselves should also be aware of these influential factors and express their needs accordingly. In line with "The appropriate technical guidelines for prevention and control of myopia in children and adolescents (update version)"(*10*), which provides detailed, comprehensive interventions for individuals, families, schools, medical and health institutions, government departments, media, and social groups, this study provides supporting evidence for these guidelines. Furthermore, its findings emphasize the benefits of implementing multiple-level comprehensive interventions, especially among younger children (*10*).

This study had several limitations that need to be acknowledged. First, the definition and measurement of myopia used in this study, although acceptable for population assessment, may not be considered the gold standard for clinical diagnosis. Unfortunately, conducting cycloplegic refraction was not feasible due to the large sample size. Second, the measurement of outdoor time and other modifiable factors relied on questionnaires, which may introduce recall bias and self-reporting bias. Third, the relatively short six-month interval between the two waves of follow-up may have limited the ability to demonstrate the significant protective effect of some modifiable factors, such as outdoor time, which has been confirmed in other studies. Fourth, the small sample size of grade 7–11 children might have influenced the statistical power of the analysis. Lastly, this study's statistical strategy required the dichotomization of each modifiable factor, which reduced the statistical efficiency of the analysis.

Myopia prevention among children and adolescents is a complex undertaking that necessitates comprehensive interventions and collaborative efforts from schools, families, children themselves, governments, and society as a whole.

Conflicts of interest: No conflicts of interest.

Funding: Supported by the China Medical Board (Grant #21-434 to YS) and Capital's Funds for Health Improvement and Research (2022-1G-4251 to YS).

doi: 10.46234/ccdcw2024.031

[#] Corresponding author: Yi Song, songyi@bjmu.edu.cn.

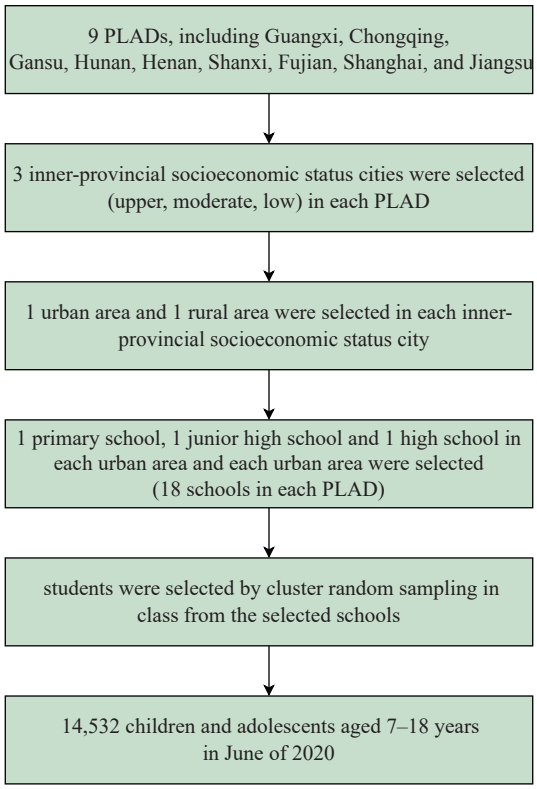
[1] Institute of Child and Adolescent Health, School of Public Health, Peking University; National Health Commission Key Laboratory of

Reproductive Health, Beijing, China; [2] Department of Sport, Physical Education & Health, Hong Kong Baptist University, Kowloon Tong, Hong Kong Special Administrative Region, China; [3] Department of Medicine, Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, United States.

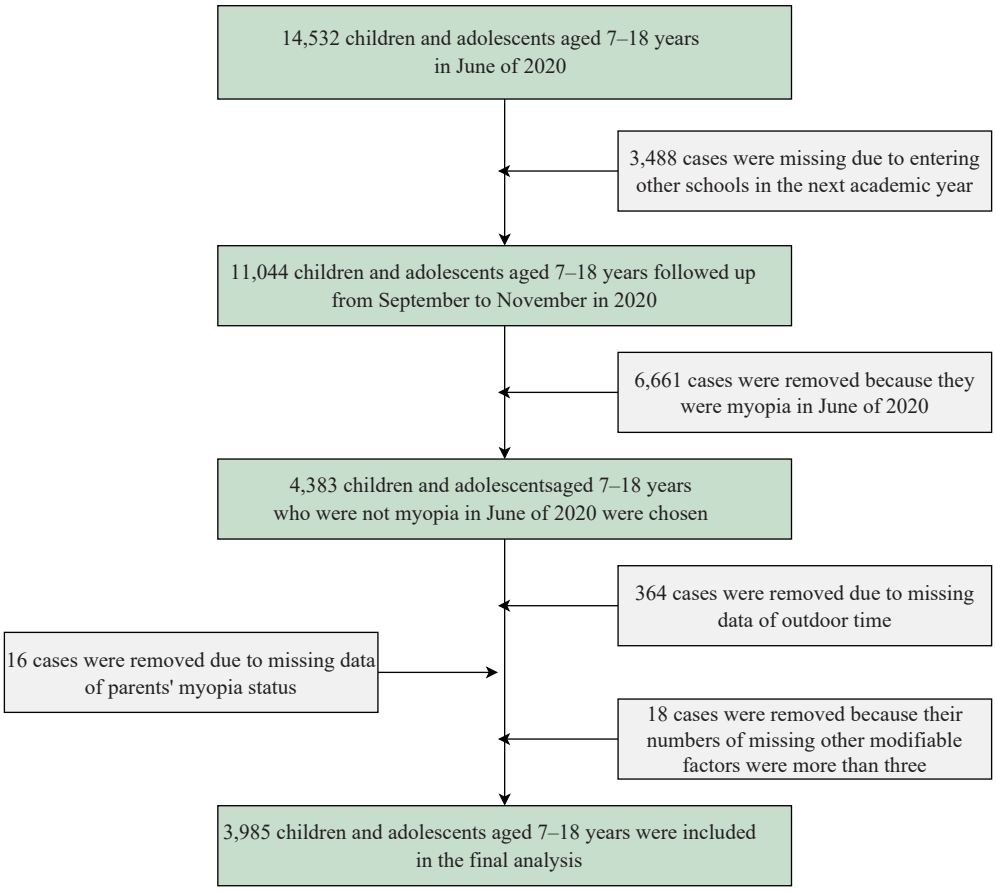
Submitted: September 28, 2023; Accepted: January 09, 2024

REFERENCES

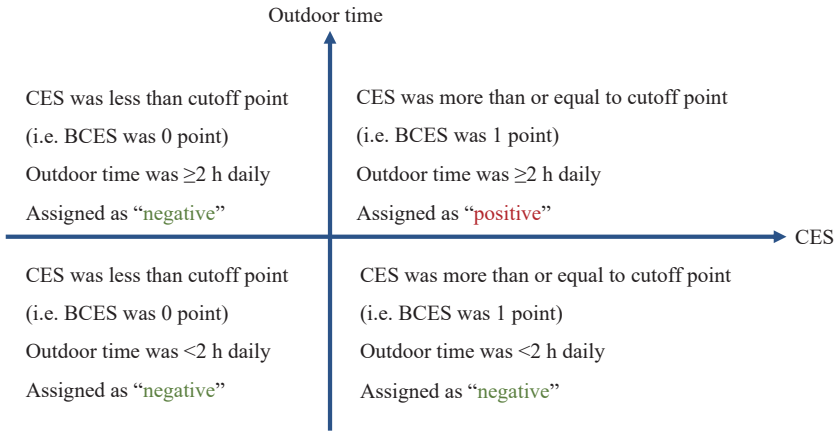
1. Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 2016;123(5):1036 – 42. https://doi.org/10.1016/j.ophtha.2016.01.006.
2. Qiao J, Wang YY, Li XH, Jiang F, Zhang YT, Ma J, et al. A Lancet Commission on 70 years of women's reproductive, maternal, newborn, child, and adolescent health in China. Lancet 2021;397(10293):2497 – 536. https://doi.org/10.1016/s0140-6736(20)32708-2.
3. Ministry of Education and other seven departments. the Comprehensive National Children's Myopia Management Plan. 2018. http://www.moe.gov.cn/srcsite/A17/moe_943/s3285/201808/t20180830_346672.html. [2023-09-05]. (In Chinese).
4. Jan C, Li L, Keay L, Stafford RS, Congdon N, Morgan I. Prevention of myopia, China. Bull World Health Organ 2020;98(6):435 – 7. https://doi.org/10.2471/blt.19.240903.
5. Morgan IG, Wu PC, Ostrin LA, Tideman JWL, Yam JC, Lan WZ, et al. IMI Risk Factors for Myopia. Invest Ophthalmol Vis Sci 2021;62(5):3. https://doi.org/10.1167/iovs.62.5.3.
6. Dong YH, Jan C, Chen L, Ma T, Liu JY, Zhang Y, et al. The cumulative effect of multilevel factors on myopia prevalence, incidence, and progression among children and adolescents in China during the COVID-19 pandemic. Transl Vis Sci Technol 2022;11(12):9. https://doi.org/10.1167/tvst.11.12.9.
7. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396(10258):1223 – 49. https://doi.org/10.1016/s0140-6736(20)30752-2.
8. Morgan IG, French AN, Ashby RS, Guo XX, Ding XH, He MG, et al. The epidemics of myopia: Aetiology and prevention. Prog Retin Eye Res 2018;62:134 – 49. https://doi.org/10.1016/j.preteyeres.2017.09.004.
9. Rose KA, French AN, Morgan IG. Environmental factors and myopia: paradoxes and prospects for prevention. Asia Pac J Ophthalmol (Phila) 2016;5(6):403 – 10. https://doi.org/10.1097/apo.0000000000000233.
10. National Health Commission of the People's Republic of China. the appropriate technical guidelines for prevention and control of myopia in children and adolescents (update version). 2021. http://www.nhc.gov.cn/jkj/s5899tg/202110/65a3a99c42a84e3f8a11f392d9fea91e.shtml. [2023-09-05]. (In Chinese).



SUPPLEMENTARY FIGURE S1. Sampling frame of the data.
Abbreviation: PLAD=Provincial-level administrative division.



SUPPLEMENTARY FIGURE S2. Data screening flow chart.



SUPPLEMENTARY FIGURE S3. Definition of the combined effect of outdoor time and modifiable factors.
Note: Cutoff points ranged from 3 to 8.
Abbreviation: CES=cumulative effect score; BCES=binary cumulative effect score.

Preplanned Studies

Analysis of Hot Topics Regarding Global Smart Elderly Care Research — 1997–2021

Hongman Wang[1,#]; Hong Chen[2]; Yuqi Wang[1]

Summary

What is already known about this topic?

With the assistance of the internet, big data, cloud computing, and other technologies, the concept of smart elderly care has emerged.

What is added by this report?

This study presents information on the countries or regions that have conducted research on smart elderly care, as well as identifies global hotspots and development trends in this field.

What are the implications for public health practice?

The results of this study suggest that future research should focus on fall detection, health monitoring, and guidance systems that are user-friendly and contribute to the creation of smarter safer communities for the well-being of the elderly.

Population aging has become a significant global concern due to increased life expectancy and reduced fertility rates. According to United Nations data (*1*), the number of individuals aged 65 and above worldwide reached 727 million in 2020. Over the next three decades, this number is expected to more than double, surpassing 1.5 billion in 2050. The proportion of elderly individuals in the global population is projected to increase from 9.3% in 2020 to 16.0% in 2050. By mid-century, one in six individuals worldwide will be 65 years or older. This demographic shift necessitates well-planned healthcare and social systems to support the well-being of the elderly as they age. The advancement of technologies such as the Internet of Things, cloud computing, and blockchain has given rise to smart elderly care, which can provide personalized health services through the integration of big data and a one-health approach. Smart elderly care is crucial for promoting active and healthy aging (*2*). It relies on foundational technologies like the Internet of Things, big data, artificial intelligence, and blockchain, with smart communities, cities, and societies serving as support. Third-party professional service organizations play a crucial role in ensuring the effectiveness of smart elderly care. By integrating resources and employing unified resource scheduling, this new model of care enables efficient data interconnection (*3*). To examine the key areas of research in smart elderly care, this paper utilizes bibliometric analysis.

This study focuses on the interdisciplinary field of smart elderly care, which encompasses disciplines such as sociology, medicine, computer science, electronic information engineering, management, economics, and law. To conduct a bibliometric analysis, we utilized the Web of Science (WOS) Core Collection, a comprehensive database covering these disciplines (the time range of literature included in this database has been from 1900 onwards). A search formula was employed: "TS=(smart elderly care) OR TS=(smart care for elderly) OR TS=(smart care for aged) OR TS=(smart senior care) OR TS=(intelligent old-age care) OR TS=(intelligent elderly care) OR TS=(intelligent senior care) OR TS=(intelligent elderly support)." This search was conducted from January 1, 1900, to October 31, 2021, and resulted in a total of 2,141 retrieved papers. The literature was then screened by reviewing titles, keywords, and abstracts. After removing duplicates, news articles, reviews, and publications unrelated to the research theme "smart elderly care," we included a final set of 1,699 valid literature for analysis.

This study utilizes bibliometrics to analyze the literature and provide insights into the current research status in the field of smart elderly care. The publication date, country, and frequently occurring keywords in the literature are sorted and analyzed using SATI (version 3.2; Qiyuan Liu & Ying Ye, Hangzhou, China), COOC (version 9.9; XueShuDianDi, Beijing, China), and Excel software (version 2019; Microsoft, Washington State, USA). Specifically, SATI software is used to extract and analyze information such as publication time, country, and keywords. Excel software is employed for data analysis, while COOC is utilized to generate knowledge maps.

A total of 1,699 valid documents were analyzed to

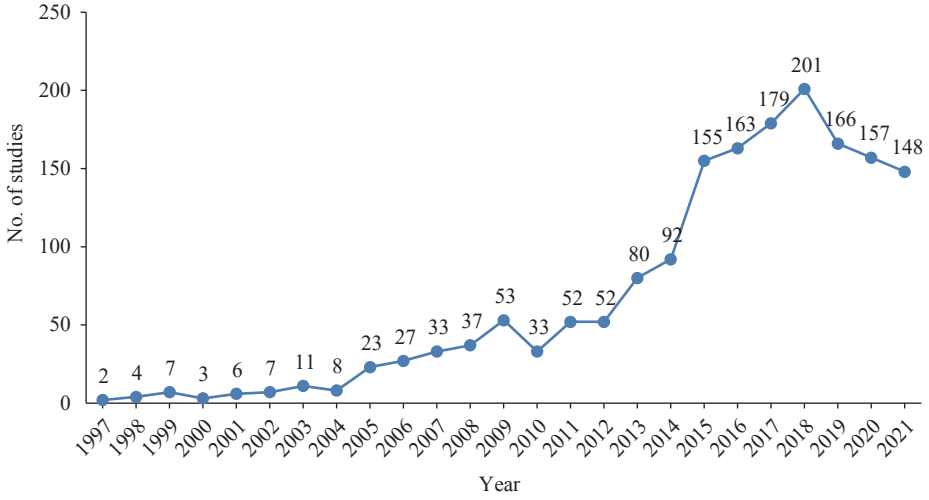


FIGURE 1. The number of studies in English on smart elderly care by year 1997–2021.

examine the temporal distribution of English literature on smart elderly care, as depicted in Figure 1. Based on the analysis, the research on smart elderly care can be divided into two stages. The first stage covers the period from 1997 to 2014, during which less than 100 articles were published annually. Subsequently, from 2015 to 2021, the number of articles published increased significantly, with over 100 articles per year. In 2018, the number peaked at 201 and then started fluctuating. A total of 99 countries worldwide have conducted research on smart elderly care, with China ranking first. The top 10 countries are presented in Table 1.

The SATI software was utilized to extract and clean keywords. The cleaning principles involved merging synonyms, such as replacing "senior citizens," "older adults," "older people," "aged," and "elderly" with "elderly people." Additionally, incomplete concept expressions were supplemented, for example, "AAL" was replaced with "Ambient Assisted Living." Abstract words, such as "overview," were deleted. Following these principles, a total of 4,058 keywords were extracted from 2,141 literature. Table 2 presents the high-frequency keywords (frequencies greater than 15). Co-occurrence analysis was performed on these high-frequency keywords, resulting in the co-occurrence graph displayed in Figure 2. The analysis identified five dimensions, each represented by a different color in Figure 2.

TABLE 1. Top 10 countries with smart elderly care research 1900–2021.

No.	Countries	Number of papers
1	China	299
2	USA	225
3	England	118
4	Japan	110
5	Spain	103
6	Italy	97
7	India	75
8	Germany	68
9	Australia	64
10	France	49

DISCUSSION

This study identified five main research areas within the field of smart elderly care. The first area focuses on smart home technologies, which aim to enhance the quality of life for the elderly. The keywords associated with this dimension include smart home, ambient assisted living, elderly care, activity recognition, ambient intelligence, pervasive computing, wireless sensor network, assisted living, Radio Frequency Identification (RFID), activities of daily living, and human-robot interaction. These keywords highlight the importance of creating a smart living environment for the elderly, utilizing various technologies to improve their overall well-being and daily functioning.

In a related study, Calatrava-Nicolás, et al. (*4*) developed a robotic-based health monitoring and guidance system for the elderly. This system incorporates intelligent sensors, actuators, and a robot platform to interact with the users, providing environmental intelligence. By leveraging robotics and artificial intelligence, this system addresses the mental health needs of the elderly, assisting them in their daily

TABLE 2. High-frequency keywords of smart elderly care research (frequency ≥15)

No.	Keywords	Frequency	No.	Keywords	Frequency
1	Smart home	239	22	Technology	26
2	Elderly people	162	23	RFID	23
3	Internet of things	156	24	Monitoring	22
4	Ambient assisted living	107	25	Home care	21
5	Elderly care	91	26	Aging in place	21
6	Activity recognition	80	27	Wearable sensors	19
7	Healthcare	69	28	Health monitoring	19
8	Fall detection	63	29	Quality of life	19
9	Machine learning	55	30	Independent living	19
10	e-health	46	31	Remote monitoring	18
11	Assistive technology	43	32	Cloud computing	18
12	Telemedicine	42	33	Smart healthcare	17
13	Ambient intelligence	38	34	Assistive technologies	17
14	Aging	38	35	Activities of daily living	17
15	Dementia	35	36	Big data	17
16	Pervasive computing	34	37	Smart cities	17
17	Artificial intelligence	32	38	Human-robot interaction	17
18	Wireless sensor network	31	39	Privacy	16
19	Deep learning	31	40	Telehealth	16
20	Sensors	30	41	Intelligent systems	15
21	Assisted living	28			

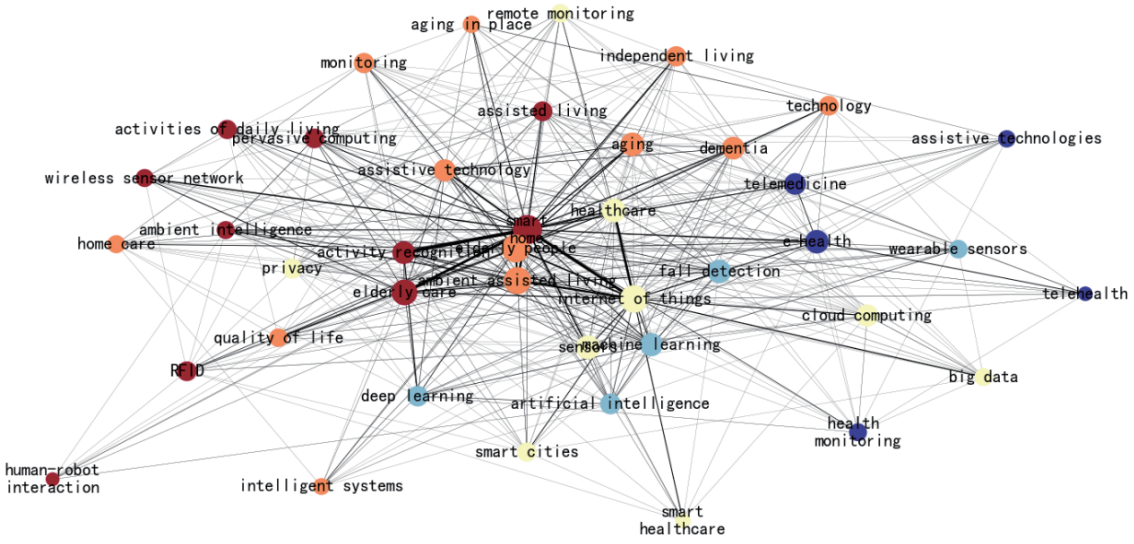


FIGURE 2. Co-occurrence of high-frequency keywords in research on smart elderly care.

activities. The second dimension of our study centers around the concept of "aging in place." It involves the use of intelligent devices to support elderly individuals in remaining in their familiar living environment during their later years. The key focus areas include elderly people, assistive technology, aging, dementia, technology, monitoring, home care, aging in place, independent living, and quality of life. These keywords highlight our emphasis on promoting independent living and enhancing the quality of life for the elderly

through the use of assistive technology.

According to the World Health Organization (WHO) (*5*), aging in place allows elderly individuals to stay in their familiar living environment, maximize their independence, and ensure a good quality of life during their later years. This approach also helps to reduce the economic burden associated with other forms of elderly support.

The third dimension of this study examines the utilization of information technology in the field of elderly medical care. The dimension includes 9 key terms: internet of things, healthcare, sensors, cloud computing, remote monitoring, smart cities, big data, smart healthcare, and privacy. Specifically, within the context of smart cities, these key terms primarily focus on the application of information technology such as internet of things, cloud computing, and big data in elderly healthcare, with an emphasis on privacy concerns. Kor AL, et al. (*6*) have developed the SMART-Item system, which leverages cloud computing and internet of things technologies. This system provides intelligent medical and nursing care for the elderly, encompassing the entire data lifecycle, including acquisition, transmission, integration, processing, computation, visualization, intelligence analysis, data sharing, and storage. The SMART-Item system offers a comprehensive integrated intelligent service.

The fourth dimension of our study focuses on fall monitoring, specifically exploring the following six key areas: fall detection, machine learning, artificial intelligence, deep learning, wearable sensors, and intelligent systems. These keywords are essential in understanding the application of various artificial intelligence technologies in monitoring falls among the elderly population. Koshmak et al. (*7*) conducted research utilizing cell phone technology combined with physiological data detection in novice skaters to collect fall data. The study's findings indicated that the online algorithm exhibited a specificity of 90%, a sensitivity of 100%, and an accuracy of 94%. In a separate study, Shiba et al. (*8*) investigated a fall detection system based on microwave Doppler sensors. The system successfully detected multiple fall scenarios, including tripping, slipping, coma, walking, bending, sitting, and standing. The accuracy, positive predictive value, and negative predictive value of the system were determined to be 0.95, 0.94, and 0.97, respectively.

The fifth dimension of our study focuses on health monitoring, encompassing the following key terms: e-health, telemedicine, health monitoring, assistive technologies, and telehealth. The aim is to explore the application of telemedicine technologies in monitoring the health of older adults. One study conducted by DanaKai Bradford (*9*) examined the Smarter Safer Homes project, which aims to develop a platform for monitoring the safety, physical health, and brain function of the elderly. This platform utilizes sensory information from the environment, cognition, physical activity, and physiology to assess the health status of older adults and determine the need for medical intervention. Another study by Larkai DL, et al. (*10*) focused on remote heart rate monitors as part of a personal emergency response system. These monitors can detect abnormal heart rates in real-time and promptly notify authorized clinicians in emergency situations.

The articles analyzed were only retrieved from the WOS. Research published in other databases was not considered, and the majority of the articles were in English. This may result in the omission of significant research conducted in other languages. However, WOS primarily focuses on academic papers in the interdisciplinary fields of sociology and medicine, which still allows for a comprehensive understanding of the current hot topics in global smart elderly care research.

The aging population is a significant social and economic challenge worldwide. It is important to address this issue promptly by leveraging technologies such as the internet, big data, and cloud computing to develop smart elderly care solutions. Despite the growing number of publications on this topic, there has been no comprehensive review of the research landscape and its impact on global smart elderly care. Therefore, this study aims to investigate global research in this field and identifies five key dimensions. Moving forward, there is a need for more in-depth research in smart elderly care that focuses on user-friendly aspects such as high accuracy, precision, ease of use, and ethical considerations to ensure the well-being of seniors. It is noteworthy that among the top 10 countries with the most publications, China (ranking first) is the only developing country. Thus, we encourage scholars from developing countries to actively participate in the discourse on smart elderly care and healthy aging.

Conflicts of interest: No conflicts of interest.

Funding: Supported by Beijing Returned Overseas Chinese Federation (20220125).

doi: 10.46234/ccdcw2024.032

[#] Corresponding author: Hongman Wang, pkuwhm2006@163.com.

[1] School of Health Humanities, Peking University, Beijing, China; [2] Center for Global Public Health, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: November 29, 2023; Accepted: February 21, 2024

REFERENCES

1. United Nations. World population ageing 2020 highlights. 2021. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/undesa_pd-2020_world_population_ageing_highlights.pdf. [2023-10-15].
2. Wang HM, Chen H. Aging in China: challenges and opportunities. China CDC Wkly 2022;4(27):601 – 2. https://doi.org/10.46234/ccdcw2022.130.
3. Wang HM. Blue book of elderly health: research and policy implementation of healthy aging in China. Beijing: Chinese Financial & Economic Publishing House. 2020.
4. Calatrava-Nicolás FM, Gutiérrez-Maestro E, Bautista-Salinas D, Ortiz FJ, González JR, Vera-Repullo JA, et al. Robotic-based well-being monitoring and coaching system for the elderly in their daily activities. Sensors 2021;21(20):6865. https://doi.org/10.3390/s21206865.
5. World Health Organization. Integrated care for older people: guidelines on community-level interventions to manage declines in intrinsic capacity. 2017. https://apps.who.int/iris/handle/10665/258981. [2023-10-1].
6. Kor AL, Yanovsky M, Pattinson C, Kharchenko V. SMART-ITEM: IoT-enabled smart living. In: 2016 future technologies conference (FTC). San Francisco: IEEE. 2016; p. 739-49. https://doi.org/10.1109/FTC.2016.7821687.
7. Koshmak GA, Linden M, Loutfi A. Evaluation of the android-based fall detection system with physiological data monitoring. In: 2013 35th annual international conference of the IEEE engineering in medicine and biology society (EMBC). Osaka: IEEE. 2013; p. 1164-8. http://dx.doi.org/10.1109/EMBC.2013.6609713.
8. Shiba K, Kaburagi T, Kurihara Y. Fall detection utilizing frequency distribution trajectory by microwave Doppler sensor. IEEE Sens J 2017;17(22):7561 – 8. https://doi.org/10.1109/JSEN.2017.2760911.
9. Bradford D. Detecting degeneration: monitoring cognitive health in independent elders. In: 2013 35th annual international conference of the IEEE engineering in medicine and biology society. Osaka: IEEE. 2013; p. 7029-32. http://dx.doi.org/10.1109/EMBC.2013.6611176.
10. Larkai DL, Wu RH. Wireless heart rate monitor in personal emergency response system. In: 2015 IEEE 18th international symposium on design and diagnostics of electronic circuits & systems. Belgrade: IEEE. 2015; p. 299-300. http://dx.doi.org/10.1109/DDECS.2015.70.

Preplanned Studies

Inflection Point Age in the Middle and Older Women — Jiangxi Province, China, 2020–2022

Shanlan Yang[1,2]; Langlang Zhang[3]; Helang Huang[3]; Jiaofeng Wang[2]; Lei Wu[3,#]; Zhijun Bao[1,2,#]

Summary

What is already known about this topic?

Previous studies have predominantly examined the micro-level aspects of women aging inflection points, while macro-level research using big data on the inflection points of aging among middle-aged and elderly women in China is currently limited.

What is added by this report?

This study determined the inflection ages for physiological, psychological, social, and total dimensions in middle-aged, young elderly, and elderly women [(48.0–53.2) *vs.* (66.3–70.0) *vs.* (78.4–81.2) years old].

What are the implications for public health practice?

This study is important for gaining a deeper understanding of aging, identifying patterns of aging, and implementing targeted interventions to promote the overall health of Chinese women.

Numerous studies in the fields of life sciences and epidemiology have demonstrated that women differ significantly from men in terms of physiology, psychology, and social function. Moreover, the aging process and its mechanisms vary between genders, with women being more susceptible to aging and more interested in preventive measures (*1*–*2*). The concept of the longevity inflection point proposes that there is a specific stage in life where degenerative changes occur (*3*). As a result, research investigating changes in women aging at a microscopic level has emerged in recent years. Predicting the aging process and identifying the inflection point through biomarker analysis has become a prominent research trend. However, these microscopic studies have limitations, including small sample sizes and high workloads. In this study, we conducted a comprehensive assessment of the aging level among middle-aged and elderly women in Jiangxi Province, China, from January 2020 to December 2022. We utilized big data epidemiological surveys and employed statistical analysis through numerical modeling to calculate the inflection ages in the physiological, psychological, social, and overall dimensions for middle-aged, young, and elderly women [(48.0–53.2) *vs.* (66.3–70.0) *vs.* (78.4–81.2) years old].

Based on the recent gross domestic product (GDP) level and social development status of Jiangxi Province, nine urban and rural communities that meet the specified criteria were selected as research sites for this project. A multi-stage stratified cluster sampling approach was employed, following the county-district-community three-level management model. The final sampling was conducted at each community health service center. The inclusion criteria for the study were as follows: 1) Women aged 40 years or older who have resided in Jiangxi Province for more than three years; 2) Women who can actively participate in the study, cooperate with the survey, and provide the required information; 3) The sampling proportion for different age groups should not exceed the proportion of the age composition of the women population in Jiangxi Province. Exclusion criteria included individuals with serious illness, disabilities, mental disorders, or the inability to participate in the entire study.

In this study, we assessed an individual's level of aging using the Physiological-Psychological-Social Three-Dimensional Human Aging Scale (PPSHAS). This scale comprehensively evaluates aging in the physical, psychological, and social dimensions, encompassing factors such as wrinkles, hearing, cognition, mood, social participation, and organizational interactions. The scale produces a standardized score for the overall level of aging, which has shown excellent reliability and validity (Cronbach's α =0.930, retest reliability=0.856) (*4*).

Based on the pre-survey results (*4*), the percentage of women classified as "obviously young" ranged from 11.96% to 35.94%. The proposed median value of 23.95% was deemed to be the positive probability (p), with a bilateral test level α of 0.05 and an allowable error (δ) of 0.1p. Taking into account potential non-compliance of participants, the original sample size was

increased by 20%, resulting in a final sample size of 1,500.

Ethical clearance for this study was obtained from the Second Affiliated Hospital of Nanchang University, and participants and their legal guardians were informed about the study goals. A total of 1,785 women from nine cities were surveyed, and 1,720 valid questionnaires were collected, yielding an effective response rate of 96.36%.

According to the age groups defined by the World Health Organization (WHO), participants were categorized into three groups: middle-aged (45–59 years old), young elderly (60–74 years old), and elderly (≥75 years old). The participants were further divided into more specific age groups using the PPSHAS tools, with individuals scoring below the standardized P_{50} score for their respective age group considered not to be aging. Statistical analysis was carried out using R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria), including fitting Locally Weighted Regression smooth curves (LOESS) and conducting data analysis.

The age at which aging began was determined using the receiver operator characteristic curve (ROC) and the approximate Youden index. The binary logistic regression model was used to control for the confounding effects of education level, occupation, and marital status. The odds ratios (*OR*s) from the logistic regression model were utilized to compare the degree of aging, with an *OR*>1.000 indicating a deepening of aging beyond the inflection point age. The model's effectiveness in predicting the degree of aging was assessed using the C index. The model's consistency was evaluated using the Hosmer-Lemeshow test (α =0.05).

To ensure the reliability of the research results, all investigators underwent a strict selection process and received specialized training. Regular data checks were conducted during the survey, and all data were reviewed individually to eliminate any invalid questionnaires.

Among the 1,720 participants, the average age was 62.73±10.88 years. The age group of 65–69 accounted for the largest proportion at 17.73%. The highest education level was primary school or below at 55.58%, followed by junior high school at 25.00%. In terms of occupation, 23.72% of participants were workers, 39.77% were farmers, and 20.47% were cadres. Regarding marital status, 82.67% were married, 16.34% were widowed, and 0.99% were unmarried. In addition, 57.33% of the participants were from rural areas and 42.67% were from urban areas.

A one-way analysis of variance (ANOVA) was conducted to assess the standardized scores of aging in the physiological, psychological, social, and total dimensions. The results indicated significant differences in the standardized scores of aging degree across different age groups within the same group and between different age groups, except for the psychological dimension of middle-aged individuals. The *P* was less than 0.05 (Table 1).

We plotted scatter plots of chronological age (X) and the normalized score of aging degree in different dimensions (Y) for three age groups. The LOESS local weighted regression method was used for smoothing. Our observation indicated that the score of aging degree in the physiological, psychological, social , and overall dimensions increased in a zigzag pattern with age (Figure 1).

In the figure, the black scatter plots represent the standardized scores (Y) for different aging dimensions at each individual's chronological age (X). The blue curves represent the LOESS curve fits for the overall chronological age (X) and the standardized scores (Y) in different aging dimensions.

Based on the LOESS fitting results, we can hypothesize that there is an inflection point in the aging process at different ages. Furthermore, our analysis using the ROC curve demonstrated that, except for the psychological dimension in the young elderly group, the predictive value of the inflection point age in all dimensions was statistically significant (*P*<0.05) and had an area under the curve (AUC) greater than 0.500 (Table 2).

To investigate the predictive value of the inflection point age on the degree of aging, we conducted a binary logistic regression analysis. The dependent variable Y represented the original aging degree score (0=not aging, 1=aging), while the independent variable X represented the newly divided aging degree score (comparison group: 1=greater than inflection point age, reference group: 2=less than inflection point age). We controlled for three types of confounding effects in the analysis.

The results indicated that the *OR* values [95% confidence interval (*CI*)] were consistently greater than 1.000. This suggests that aging deepens in individuals older than the inflection point age, particularly in the physiological dimension of the elderly group. The greatest risk of aging was observed in individuals aged above 78.87 years old (*OR*=5.290). Considering the overall aging situation, the risk of aging was highest in

TABLE 1. Distribution and comparison of standardized scores of aging among different age groups in Jiangxi Province, China, 2020–2022.

Age groups	Age (years)	*N*	(%)	Dimension			Total dimension
				Physiological	Psychological	Social	
Middle-aged	≥40	221	32.74	23.77±5.50	14.59±2.47	5.15±0.94	43.51±6.99
	≥50	210	31.11	26.57±4.59	14.67±2.72	5.36±1.03	46.59±6.34
	≥55	244	36.15	28.79±4.75	14.61±2.73	5.72±2.49	49.11±6.57
	N	675	100.00	26.46±5.38	14.62±2.64	5.42±1.70	46.49±7.03
	F	–	–	54.958*	0.049	6.742	41.305
	P-value			<0.001	0.952	<0.001	<0.001
Young elderly	≥60	277	34.07	30.66±4.47	14.63±2.67	5.57±0.99	50.86±6.52
	≥65	305	37.52	32.65±4.45	14.85±2.82	5.77±1.13	53.27±6.43
	≥70	231	28.41	35.43±4.80	15.3±2.79	6.19±1.38	56.92±7.43
	N	813	100.00	32.76±4.92	14.9±2.77	5.82±1.19	53.49±7.16
	F	–	–	68.940	3.774	16.545*	50.806
	P-value			<0.001	0.023	0.001	<0.001
Elderly	≥75	119	51.29	37.24±4.97	14.78±3.12	6.46±1.58	58.48±8.20
	≥80	113	48.71	40.56±5.22	15.73±3.15	7.08±1.98	63.38±8.94
	N	232	100.00	38.86±5.35	15.24±3.16	6.76±1.81	60.86±8.90
	F	–	–	24.658	5.374	6.998	18.936
	P-value			<0.001	0.021	0.009	<0.001
N		1,720	100.00	31.11±6.67	14.84±2.78	5.79±1.56	51.74±8.82
F		–	–	576.997	4.396*	49.806*	329.209*
P-value				<0.001	0.013	<0.001	<0.001

Note: The F-distribution is approximated using the Welch method.
"–" indicates that no value is available here.
* indicates that the variance is uneven for Levene statistics.

the elderly group, followed by the middle-aged group, and lowest in the young elderly group (*OR* elderly: 4.867 >*OR* middle-aged: 4.472 >*OR* young elderly: 2.454).

Among the three age groups, the risk of aging in the social dimension was higher than that in the psychological dimension. The logistic regression model had a C-index (95% *CI*) greater than 0.700, indicating that the age of the inflection point possesses predictive value for the transition of aging. The Hosmer-Lemeshow test confirmed that the predicted results and the actual aging results for each age group were consistent (P_1>0.05), suggesting an ideal degree of model calibration (Table 3).

DISCUSSION

This study found that middle-aged and older adults, younger older adults, and older women experience accelerated aging at 48.0–53.2, 66.3–70.0, and 78.4–81.2 years of age, respectively. However, our findings do not completely align with the classical view regarding the inflection point of aging, which suggests that the peak of aging occurs at 34, 60, and 78 years of age (*5*). It is important to note that aging rates may differ among races due to variations in lifestyle characteristics, diet, and behavior between Eastern and Western populations. Nevertheless, our results are consistent with those of the Quzhou women's cohort study, which used a multicohort analysis and observed significant aging changes in women at age 50 (*6*). It should be emphasized that this particular cohort consisted of only 113 women and required substantial time and labor for physical examinations, transcriptome testing, and plasma metabolic analyses.

The aging process of middle-aged Chinese women is influenced by menopause, which typically occurs between the ages of 48 and 52. During this period, there is a decrease in estrogen secretion, leading to various physiological changes such as decreased sexual function and aging-related symptoms like hot flashes, night sweats, insomnia, anxiety, and nervousness (*7*).

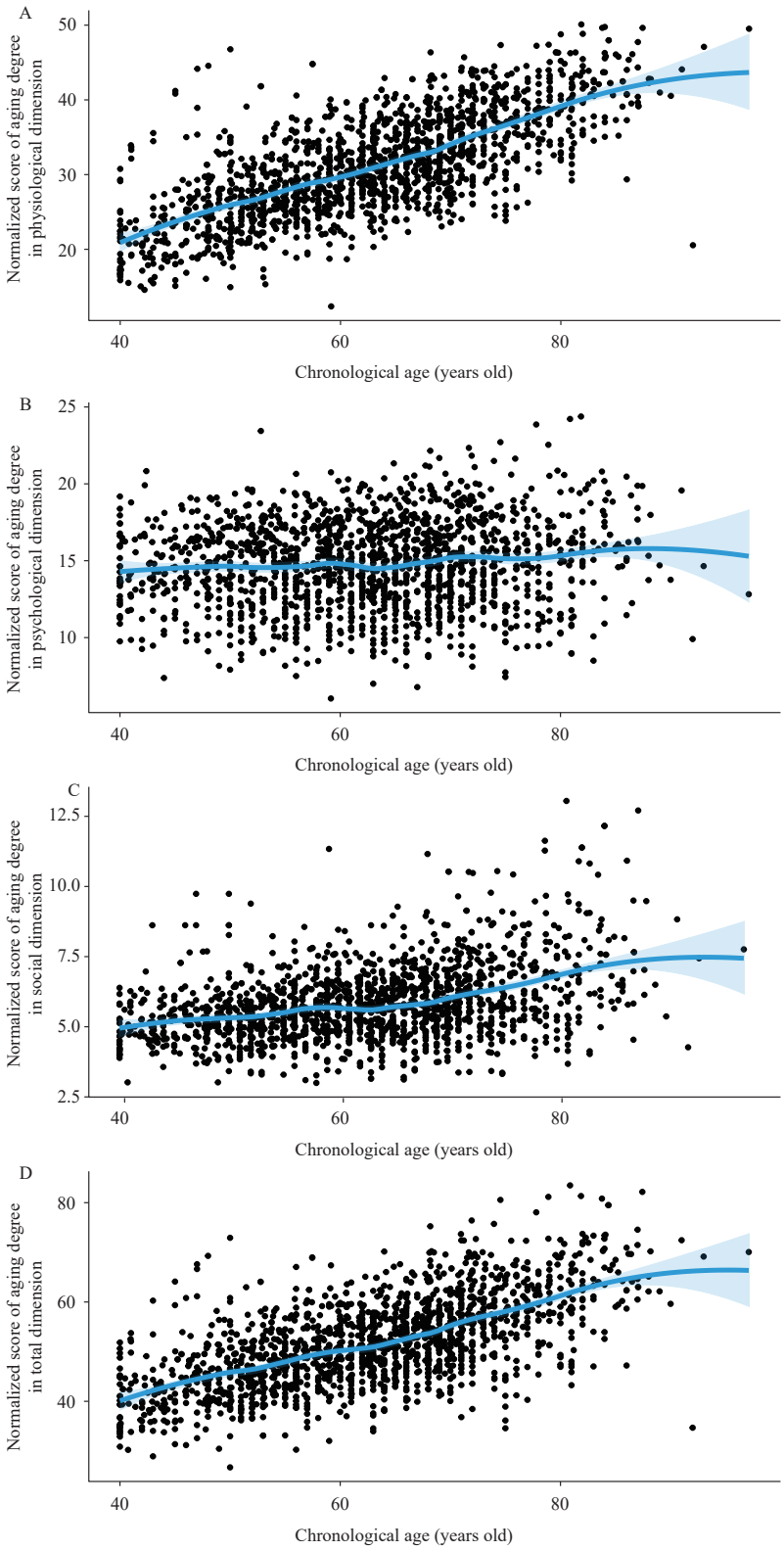


FIGURE 1. LOESS curve smoothing chart of different dimensions of aging scores among different age groups in Jiangxi Province, China, 2020–2022. (A) LOESS curve smoothing chart of physiological dimension aging score among different age groups; (B) LOESS curve smoothing chart of psychological dimension aging score among different age groups; (C) LOESS curve smoothing chart of social dimension aging score among different age groups; (D) LOESS curve smoothing chart of total dimension aging score among different age groups.
Abbreviation: LOESS=locally weighted regression.

TABLE 2. ROC analysis of aging inflection point age among different age groups in Jiangxi Province, China, 2020–2022.

Age group	Dimension	AUC (95% *CI*)	Sensitivity	Specificity	Youden index	Inflection point age	*P*-value
Middle-aged	Total	0.694 (0.658, 0.729)	0.599	0.713	0.3124	53.16	0.0001
	Physiological	0.709 (0.673, 0.743)	0.604	0.724	0.3276	53.18	0.0001
	Psychological	0.547 (0.508, 0.585)	0.789	0.311	0.1000	48.00	0.0344
	Social	0.661 (0.573, 0.648)	0.548	0.654	0.2019	53.09	0.0001
Young elderly	Total	0.658 (0.625, 0.691)	0.645	0.602	0.2473	66.33	0.0001
	Physiological	0.703 (0.670, 0.734)	0.608	0.703	0.3111	67.73	0.0001
	Psychological	0.539 (0.504, 0.574)	0.279	0.809	0.0878	70.25	0.0547
	Social	0.566 (0.531, 0.600)	0.311	0.821	0.1322	70.00	0.0011
Elderly	Total	0.697 (0.633, 0.755)	0.483	0.836	0.3190	81.20	0.0001
	Physiological	0.745 (0.684, 0.800)	0.776	0.621	0.3966	78.87	0.0001
	Psychological	0.610 (0.544, 0.674)	0.440	0.793	0.2328	81.20	0.0029
	Social	0.594 (0.528, 0.658)	0.672	0.509	0.1810	78.44	0.0118

Abbreviation: ROC=receiver operator characteristic; AUC=area under curve; *CI*=confidence interval.

TABLE 3. Logistic regression model validation results for the inflection point age of women among different age groups and dimensions in Jiangxi Province, China, 2020–2022.

Age group	Dimension	β	S.E.	Wald	*P*-value	*OR*	95% *CI*	*C*-index	95% *CI*	P_1
Middle-aged	Total	1.498	0.192	60.824	0.001	4.472	3.069, 6.516	0.782	0.749, 0.813	0.340
	Physiological	1.540	0.194	63.324	0.001	4.666	3.193, 6.819	0.786	0.753, 0.816	0.254
	Psychological	1.413	0.222	40.364	0.001	4.108	2.657, 6.353	0.766	0.733, 0.798	0.550
	Social	1.436	0.191	56.745	0.001	4.203	2.893, 6.107	0.779	0.745, 0.809	0.322
Young elderly	Total	0.898	0.162	30.734	0.001	2.454	1.787, 3.371	0.775	0.745, 0.803	0.833
	Physiological	0.893	0.163	29.966	0.001	2.442	1.774, 3.361	0.773	0.743, 0.802	0.305
	Social	1.582	0.364	18.923	0.001	4.867	2.386, 9.929	0.800	0.743, 0.850	0.255
Elderly	Total	1.666	0.360	21.375	0.001	5.290	2.611, 10.720	0.809	0.753, 0.858	0.756
	Physiological	1.582	0.364	18.923	0.001	4.867	2.386, 9.929	0.800	0.743, 0.850	0.255
	Psychological	1.604	0.356	20.269	0.001	4.974	2.474, 10.001	0.807	0.750, 0.855	0.744
	Social	1.498	0.192	60.824	0.001	4.472	3.069, 6.516	0.782	0.749, 0.813	0.340

Abbreviation: *OR*=odds ratio; *CI*=confidence interval.

Furthermore, aging among younger elderly women occurs before the age of 70, which reinforces societal biases and stereotypes associated with being "old and useless." Retirement often leads to increased responsibilities and stress, reduced leisure time, and limited socialization, all of which can have negative effects on their physical and mental well-being, thus accelerating the aging process (*8*).

A study has shown that women falls are most common among those aged 75 to 85 (*9*). These falls often lead to a fear of falling (*10*), and they account for 45.24% of women injury-related deaths in China (*11*). This serious decline in quality of life and functional abilities further emphasizes the impact of aging (*9*).

This study has several limitations. First, our survey only included community-based women residents in Jiangxi Province and did not include hospitalized elderly women. As a result, the actual inflection point of aging may be underestimated in the findings of this study. Additionally, the sample size of elderly women in our survey was small, leading to potential errors and limiting the generalizability of our results. Therefore, further studies with larger sample sizes are needed to calculate the inflection point ages separately for urban and rural women. These future studies should also consider the short-term effects of diseases on aging.

Despite these limitations, our findings are robust for several reasons. First, our study encompassed a large and representative sample, across various regions with different GDP levels in Jiangxi Province. This allows for a comprehensive understanding of the population aging phenomenon in the area. Second, we carefully

controlled for confounding factors when fitting our mathematical model, ensuring accurate and reliable results. Lastly, our study adopted a macro-level approach, and the obtained results align with contemporary micro studies. This not only makes our study feasible but also adds validity to our findings. In conclusion, our research contributes to a deeper understanding of aging and the natural laws governing it. It also provides valuable insights for implementing preventive measures against aging in middle-aged and elderly women.

Conflicts of interest: No conflicts of interests.

Funding: Supported by the National Key R&D Program of China (2018YFC2002000, 2018YFC2002002, 2020YFC2002901); National Natural Science Foundation of China (82071581, 81960620 and 81360446 to HH, 81960611, 81560550 to LW); Shanghai Municipal Health Commission (2021WB04, 201940415, JKKPYL-2022-15); Key Discipline Projects of Huadong Hospital (LCZX2202); Excellent Talent Projects of Huadong Hospital (HDGG2017018).

doi: 10.46234/ccdcw2024.033

[#] Corresponding authors: Lei Wu: leiwu@ncu.edu.cn; Zhijun Bao: zhijunbao@fudan.edu.cn.

[1] Shanghai Institute of Infectious Disease and Biosecurity, Fudan University, Shanghai, China; [2] Department of Gerontology, Huadong Hospital Affiliated to Fudan University, Shanghai Key Laboratory of Clinical Geriatric Medicine, Research Center on Aging and Medicine, Fudan University, Shanghai, China; [3] Jiangxi Provincial Key Laboratory of Preventive Medicine, School of Public Health, Nanchang University, Nanchang City, Jiangxi Province, China.

Submitted: November 28, 2023; Accepted: January 09, 2024

REFERENCES

1. Wang W, Zheng YX, Sun SH, Li W, Song MS, Ji QZ, et al. A genome-wide CRISPR-based screen identifies *KAT7* as a driver of cellular senescence. Sci Transl Med 2021;13(575):eabd2655. https://doi.org/10.1126/scitranslmed.abd2655.
2. Ning P, Du EQ, Du CJ, Meng QH, Wu BY. Prevalence of the disability and inflection point age of the disability level change, Shandong Province. Mod Pre Med 2020;47(9):1633-6,1664. https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjMwODMxEg94ZHlmeXgyMDIwMDkwMjQaCHZ5NnNhZW85. (In Chinese).
3. Mu GZ. "Longevity inflection point", tell us what. World Aff 2016;(8):13. https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjMwODMxEhdRS0MyMDE2MjAxNjA1MTgwMDAzNjYwNBoIaGljam1ydG8%3D. (In Chinese).
4. Wei Y, Liu X, Li X, He ZQ, Wu L, Zhou JM, et al. Physiological - psycho - social three dimensional aging index and scale construction. Chi J Dis Control Prev 2020;24(1):67 – 72. https://doi.org/10.16462/j.cnki.zhjbkz.2020.01.014.
5. Lehallier B, Gate D, Schaum N, Nanasi T, Lee SE, Yousef H, et al. Undulating changes in human plasma proteome profiles across the lifespan. Nat Med 2019;25(12):1843 – 50. https://doi.org/10.1038/s41591-019-0673-2.
6. Li JM, Xiong MZ, Fu XH, Fan YL, Dong C, Sun XY, et al. Determining a multimodal aging clock in a cohort of Chinese women. Med 2023;4(11):825 – 48.e13. https://doi.org/10.1016/j.medj.2023.06.010.
7. Lou Z, Huang YZ, Zhou JH. Research progress on the association between natural menopausal age and cardiovascular disease. Chi J Pract Gynecol Obstet 2022;38(4):462-5. http://dx.doi.org/10.19538/j.fk2022040118. (In Chinese).
8. Song J, Wang JW, Qin TT. A study on relationship between grandchildren care and working for Chinese elderly. Popul Econ 2018(3):92 – 103. https://doi.org/10.3969/j.issn.1000-4149.2018.03.009.
9. Su QQ, Mao YZ, Song M, Ku HA, Wu HY, Pi HY. Current situation of falls among older adults living in senior apartments and the influencing factors. J Nurs Sci 2022;37(12):16-8. https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjMwODMxEg5obHh6ejIwMjIxMjAwNBoIZ2locGtveHY%3D. (In Chinese).
10. Mao YZ, Su QQ, Song M, Pi HY. Prevalence and associated factors of fear of falling among community-dwelling elderly women. Acad Chin PLA Med Sch 2022;43(4):421-5. https://d.wanfangdata.com.cn/periodical/ChlQZXJpb2RpY2FsQ0hJTmV3UzIwMjMwODMxEhFqeWp4eHl4YjIwMjIwNDAxMBoIOGptNmp6b2E%3D. (In Chinese).
11. Yang SL, Tu JX, Zhu X, Zhang LL, Deng LF, Huang HL, et al. Older adult injury mortality in China: a meta-analysis. Chin J Evidence-Based Med 2022;22(12):1393-9. https://kns.cnki.net/kcms2/article/abstract?v=vCcGnC-OR20ThYZh56eWofN6IdCdqgEGoqUYmORtJRzujMMVIJiPFBdokidhyYaWCTLNTqA7tjeIgJAVl4aPA0FFqNv4dWuGIIaGRX4ppaBZy3dOnfvpH8qcC-GrsIqoAa2Znbbo0W8T7DC5nG9s0A==&uniplatform=NZKPT&language=CHS. (In Chinese).

Methods and Applications

Genetic Insights into Glycine's Protective Role Against CAD — European and East Asia, 2015 and 2020

Jiaying Yu[1,2,&]; Zhuolin Zhu[3,&]; Ting Wang[1,2]; Yuanhao Wei[1,2]; Lianjie Huang[1,2]; Qianru Zhang[1,2]; Yuting Zhang[1,2]; Yiran Wang[1,2]; Guiyou Liu[4]; Xiang Shu[5,#]; Rennan Feng[1,2,#]

ABSTRACT

Introduction: The purpose of this study is to examine the potential causal relationship between levels of circulating glycine and coronary artery disease (CAD) using a two-step Mendelian randomization (MR) analysis.

Methods: We analyzed data from genome-wide association studies (GWAS) conducted on European and East Asian populations. To assess the causal effects of circulating glycine levels on the risk of CAD. We used the inverse-variance weighting (IVW), weighted median (WM), MR-Egger, and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) methods. Furthermore, we conducted mediation analysis to investigate the contribution of blood pressure and other cardiovascular disease-related traits.

Results: The two-step Mendelian randomization analysis revealed that higher levels of glycine in the blood were associated with a reduced risk of CAD in Europeans [odds ratio (*OR*)=0.84, 95% confidence interval (*CI*): 0.72, −0.98; *P*=0.029] and East Asians: (*OR*=0.76, 95% *CI*: 0.66, −0.89; $P=3.57\times10^{-4}$). Sensitivity analysis confirmed the robustness of these findings. Additionally, our results suggest that about 6.06% of the observed causal effect is mediated through genetically predicted systolic blood pressure (SBP) in the European population.

Discussion: Our results contribute to the current knowledge regarding the involvement of glycine in the progression of CAD, and provide valuable methodological insights for the prevention and treatment of this condition.

Coronary artery disease (CAD), also known as atherosclerosis or coronary heart disease, is the leading cause of global mortality (*1*). Glycine, a non-essential amino acid, plays a critical role in cell growth, immune function, antioxidant response, and anti-inflammatory processes (*2*). Previous studies have shown positive effects of glycine on cardiovascular health (*3*). The therapeutic potential of glycine for metabolic disorders and cardiovascular diseases has been proposed. However, studies investigating the association between circulating glycine levels and CAD risk have yielded inconsistent results (*4*–*6*). Therefore, the causal relationship between glycine and CAD remains controversial, and if such a relationship exists, it may be influenced by metabolic factors such as blood pressure.

Mendelian randomization (MR) is a statistical technique that uses genetic variants as instrumental variables to assess the causal impact of an exposure on an outcome (*7*). MR leverages the fact that genetic variants are randomly assigned at conception, making them immune to confounding factors typically found in observational studies. In order to explore the causal relationship between circulating glycine levels and the risk of CAD, as well as to uncover the underlying mechanisms, we conducted a comprehensive study using a two-step MR approach. This study aimed to investigate the potential causal effects of circulating glycine on CAD risk in individuals of European ancestry and East Asians.

METHODS

In the study, we analyzed the relationship between specific genetic instruments and glycine levels in the UK Biobank (UKB), which included 114,972 individuals of European descent (Nightingale Health Plc; Biomarker Quantification Version 2020) and the study conducted by Wittemans et al. (*4*), which included 30,118 individuals of European ancestry.

All details regarding the GWAS summary-level data are presented in Supplementary Table S1 (available at https://weekly.chinacdc.cn/). In order to address

potential weak instrumental bias, instrumental variables (IVs) should significantly associate with the exposure ($P<5\times10^{-8}$) and exhibit minimal linkage-disequilibrium (LD) with other single nucleotide polymorphisms (SNPs) ($R^2<0.001$) within a clump distance of 1,000 kb (Supplementary Table S2, available at https://weekly.chinacdc.cn/). By utilizing the PhenoScanner database, we identified and subsequently excluded pleiotropic SNPs that are correlated with confounding factors (Supplementary Table S2).

Our study utilized a two-step MR analysis design (Figure 1). The primary analysis was conducted using the inverse variance-weighted (IVW) method. In instances where heterogeneity was detected, we employed the IVW method with random effects. To further explore the robustness of our findings, we conducted sensitivity analyses using alternative approaches, including MR-Egger regression, the weighted median method, and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) analysis, accounting for multiple genetic variants (*8*–*9*). To assess pleiotropy, we utilized the MR-Egger intercept test and the MR-PRESSO global test. Additionally, we evaluated heterogeneity of the MR findings using Cochran's Q-statistic and the I^2 index (*10*). The MR analyses were conducted using the 'dplyr' and 'TwoSampleMR' packages in R (version 4.0.5, R foundation for statistical computing, Vienna, Austria) The threshold of statistical significance was $P<0.05$.

RESULTS

The 19 identified SNPs collectively accounted for approximately 6.5% of the variation in circulating glycine levels (R^2=6.5%). Furthermore, the F-statistic, which exceeds 18.66, indicates a low probability of weak instrument bias occurring in this study.

We utilized a panel of 18 SNPs, excluding 1 palindromic SNP with intermediate allele frequencies, to assess the correlation between genetically predicted higher circulating glycine levels and decreased risk of CAD in Europeans. The analysis revealed a significant correlation [odds ratio (*OR*)=0.84, 95% confidence interval (*CI*): (0.72, 0.98), P=0.029, $P_{\text{Cochran's Q}}$=0.018, $P_{\text{MR-PRESSO global test}}$=0.03, $P_{\text{MR-Egger intercept test}}$=0.069]. However, when using instruments consisting of 4, 3, and 1 SNPs, no significant associations were observed, despite consistently indicating the same direction of association (Figure 2A).

Out of the initial 19 SNPs, 14 were included in our East Asian-focused MR analysis using data from Biobank Japan. Five SNPs were excluded due to missing data or palindromic status. Our analysis showed a consistent protective relationship between genetically predicted glycine levels and the risk of CAD (*OR*=0.76, 95% *CI*: 0.66, 0.89; $P=3.57\times10^{-4}$, $P_{\text{Cochran's Q}}$=0.186, $P_{\text{MR-PRESSO global test}}$=0.199, $P_{\text{MR-Egger intercept test}}$=0.038), However, other IVs sets did not show a significant association, likely due to limited statistical power (Figure 2B).

We found a significant relation between higher genetically predicted circulating glycine levels and lower genetically predicted SBP (β=−0.74, 95% *CI*: −1.28, −0.20; P=0.007, $P_{\text{Cochran's Q}}$=0.196, $P_{\text{MR-PRESSO global test}}$=0.287], $P_{\text{MR-Egger intercept test}}$=0.759). Using the CPS1 and GLDC instruments, we observed consistent effects of glycine on SBP (β=−0.62, 95% *CI*: −1.19, −0.06; P=0.03, $P_{\text{Cochran's Q}}$=0.551, $P_{\text{MR-Egger intercept test}}$=0.786] (Supplementary Figure S1, available at https:// weekly.chinacdc.cn/).

Furthermore, our analysis revealed that there was a negative relationship between genetically predicted

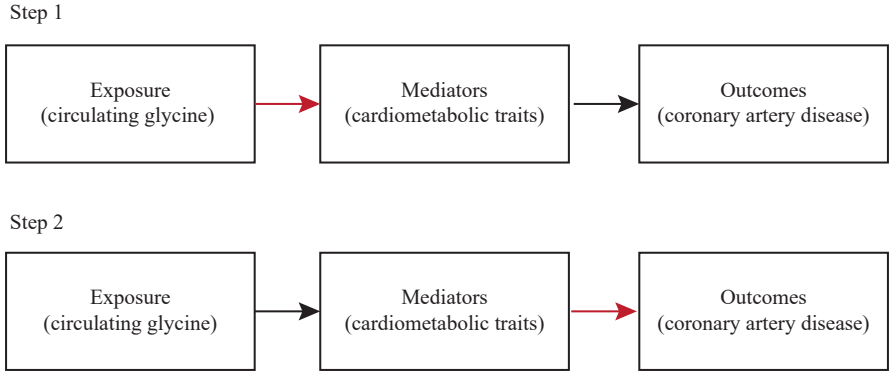


FIGURE 1. Schematic diagram of a two-step Mendelian randomization.

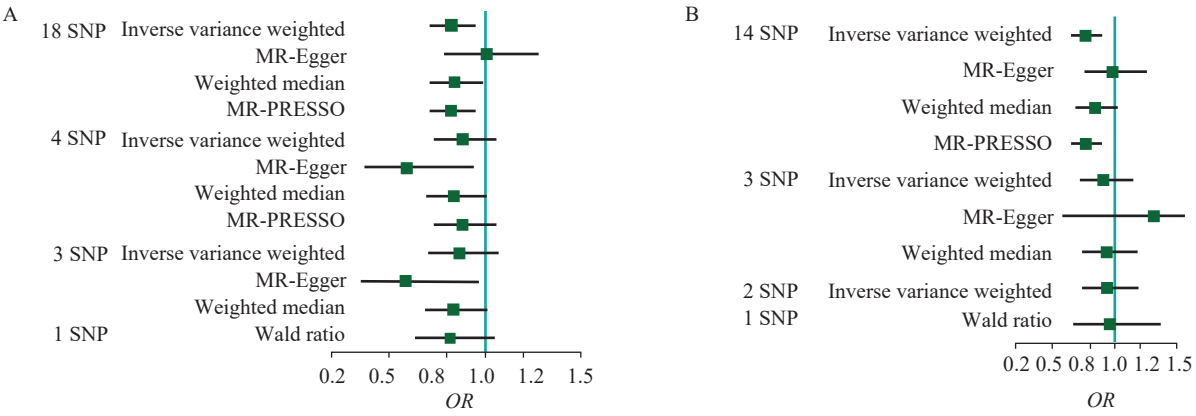


FIGURE 2. Forest plots showing effect sizes ± 95% confidence intervals for the association between genetically predicted circulating glycine levels and CAD. (A) European; (B) East Asian.
Note: Four sets of IVs were used to estimate the association between circulating glycine levels and CAD risk: 1) significant glycine-related SNPs (19 SNPs) identified in the GWAS of circulating glycine; 2) loci near genes encoding enzymes-related to glycine metabolism (GLDC, PHGDH, PSPH, ALDH1L1, and CPS1, 4 SNPs); 3) loci near genes encoding enzymes related to glycine metabolism except for the pleiotropic CPS1 locus (which showed significant associations with multiple metabolites, 3 SNPs); and 4) the loci at GCSH and GLDC encoding enzymes of the glycine cleavage system (1 SNP).
Abbreviation: SNP=single nucleotide polymorphism; MR-PRESSO=Mendelian Randomization Pleiotropy RESidual Sum and Outlier; GWAS=genome-wideassociation studies; ALDH1L1=aldehyde dehydrogenase 1 family member L1; CAD=coronary artery disease; CPS1=carbamoyl-phosphate synthase; GLDC=glycine decarboxylase; GCSH=glycine cleavage system protein H; PHGDH=phosphoglycerate dehydrogenase; PSPH=phosphoserine phosphatase; SBP=systolic blood pressure.

circulating glycine levels and genetically predicted DBP (β=−0.30, 95% *CI*: −0.56, −0.05; P=0.02, $P_{\text{Cochran's Q}}$=0.356, $P_{\text{MR-PRESSO global test}}$=0.455, $P_{\text{MR-Egger intercept test}}$=0.527). This association remained consistent when using alternative IV sets (Supplementary Figure S1, available at https://weekly.chinacdc.cn/). However, we did not find any association between predicted glycine levels and anthropometric, glycemic, inflammatory, or blood lipid traits (Supplementary Figures S2–S5, available at https://weekly.chinacdc.cn/).

Out of the 461 SNPs related to SBP, we included 412 in our MR analysis. Four SNPs were excluded due to insufficient data, and 45 SNPs were removed after an outlier test, using MR-PRESSO. We detected significant heterogeneity ($P_{\text{Cochran's Q}}$=2.17×10^{-8}), and the presence of horizontal pleiotropy was confirmed by using the MR-PRESSO global test (P<1×10^{-4}). Our results demonstrated a positive association between SBP and the risk of CAD, with each unit increase in SBP associated with a 3% increase in CAD risk (*OR*=1.03, 95% *CI*: 1.02, 1.03; P_{WM}=2.33×10^{-19}) (Table 1).

The potential mediation of systolic blood pressure (SBP) on the association between circulating glycine and CAD risk was investigated. The mediation effect involving SBP was found that 6.06% of the effect of circulating glycine, which was genetically predicted using 19 SNPs, was mediated through the genetically predicted SBP (Supplementary Table S3, available at https://weekly.chinacdc.cn/).

TABLE 1. Association of genetically predicted SBP with CAD risk in the Mendelian randomization analysis.

Method	*OR*	95% *CI*	*P*
WM	1.03	1.02 to 1.03	2.33×10^{-19}
IVW	1.03	1.03 to 1.04	1.76×10^{-56}
MR-Egger	1.04	1.03 to 1.05	1.73×10^{-11}
MR-PRESSO	1.03	1.03 to 1.04	1.96×10^{-44}

Note: *OR*>1 indicates that increased SBP was associated with an increased risk of CAD; The Cochran's Q=589.23 (P=2.17×10^{-8}), and I^2=30.24%, indicating that there was heterogeneity. The MR-PRESSO global test (P<1×10^{-4}) and MR-Egger intercept test (P=0.481) indicated that there was horizontal pleiotropy for the selected instruments.
Abbreviation: CAD=coronary artery disease; *CI*=confidence interval; MR-PRESSO=Mendelian Randomization Pleiotropy RESidual Sum and Outlier; IVW=inverse variance weighted; *OR*=odds ratio; SBP=systolic blood pressure; WM=weighted median.

DISCUSSION

The two-step MR analysis demonstrated a significant causal association between decreased levels of genetically predicted circulating glycine and CAD. Our estimation revealed that approximately 6.06% of this potential causal effect is mediated through

genetically predicted SBP, suggesting that the protective influence of circulating glycine may be attributed to its effect on reducing SBP. However, our findings suggest that other risk factors associated with CAD, such as glycemic characteristics, lipid profiles, and inflammatory markers, may not play a considerable role as mediators in this relationship.

Previous studies conducted on European white populations have produced inconsistent results regarding the association between glycine levels and the risk of developing CAD. Specifically, one study on European whites did not provide strong evidence for a causal relationship between glycine and CAD risk (*6*). Additionally, the relationship between circulating glycine levels and the CAD risk in different racial groups remains uncertain. There is only one previous study that investigated this relationship in Singaporean Chinese individuals, and reported a similar protective effect (*5*). However, this study had limitations such as a relatively small sample size and the inclusion of only two SNPs, one of which was not validated. Consequently, the study design may have compromised the validity of their findings. In our research, we have cross-validated IVs using two independent GWAS datasets, which strengthens the reliability and robustness of our conclusions.

Previous epidemiological studies have suggested that dietary glycine may have a protective effect on blood pressure regulation (*11*). Our MR analysis provides further support for this association. We found an inverse genetic correlation between circulating glycine levels and SBP, which accounted for approximately nearly 6.06% of the genetic association between glycine and CAD. In rat models of metabolic syndrome, diets rich in glycine have been shown to reduce hypertension by reducing free radical production and enhancing nitric oxide utilization (*12*). However, our study did not uncover any significant correlations between glycine and lipid traits or inflammatory markers (*13*). Further comprehensive investigations are needed to explore other potential mechanisms that may explain the genetic link between glycine and CAD.

Our study had several strengths. First, we implemented a thorough process to select valid genetic instruments for MR analysis. This procedure reduced the potential bias caused by weak instruments and improved the statistical power of our study. We used different MR methodologies to ensure the reliability of our estimates regarding the causal relationship between circulating glycine and the risk of CAD. Additionally, we conducted MR analyses on two separate populations, obtaining consistent results.

This study was subject to some limitations. First, the genetic instruments used in our analysis were derived from datasets consisting only of individuals of European descent. To date, there have been no large-scale GWAS studies investigating the relationship between circulating glycine and genetic instruments in East Asian populations. Additionally, our mediation analysis is subject to potential bias, as accurately establishing causal relationships can be challenging and distinguishing between mediation and confounding can be statistically complex.

The present study utilized MR analysis to investigate the possible causal link between serum glycine levels and CAD. These findings contribute to our understanding of the role of glycine in the development of CAD and provide methodological insights for the prevention and treatment of the disease.

Conflicts of interest: No conflicts of interest.

Acknowledgments: The study was based on the data provided by the Medical Research Council Integrative Epidemiology Unit. We thank the investigators of the previous studies.

Funding: Supported by the National Natural Science Foundation of China (82273612), and by Open Project of Key Laboratory of Science and Engineering for the Multi-Modal Prevention and Control of Major Chronic Diseases, Ministry of Industry and Information Technology (Grant No. MCD-2023-1-09).

doi: 10.46234/ccdcw2024.034

[#] Corresponding authors: Rennan Feng, fengrennan@yeah.net; Xiang Shu, shux@mskcc.org.

[1] Department of Nutrition and Food Hygiene, School of Public Health, Harbin Medical University, Harbin City, Heilongjiang Province, China; [2] Key Laboratory of Precision Nutrition and Health of Ministry of Education, School of Public Health, Harbin Medical University, Harbin City, Heilongjiang Province, China; [3] Songyang County Center for Disease Prevention and Control, Songyang City, Zhejiang Province China; [4] Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China; [5] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York City, NY, USA.
[&] Joint first authors.

Submitted: February 07, 2024; Accepted: February 22, 2024

REFERENCES

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for

the Global Burden of Disease Study 2013. Lancet 2015;385(9963): 117 – 71. https://doi.org/10.1016/S0140-6736(14)61682-2.
2. Ballevre O, Cadenhead A, Calder AG, Rees WD, Lobley GE, Fuller MF, et al. Quantitative partition of threonine oxidation in pigs: effect of dietary threonine. Am J Physiol 1990;259(4 Pt 1):E483-91. http://dx.doi.org/10.1152/ajpendo.1990.259.4.E483.
3. Razak MA, Begum PS, Viswanath B, Rajagopal S. Multifarious beneficial effect of nonessential amino acid, glycine: a review. Oxid Med Cell Longev 2017;2017:1716701. https://doi.org/10.1155/2017/1716701.
4. Wittemans LBL, Lotta LA, Oliver-Williams C, Stewart ID, Surendran P, Karthikeyan S, et al. Assessing the causal association of glycine with risk of cardio-metabolic diseases. Nat Commun 2019;10(1):1060. https://doi.org/10.1038/s41467-019-08936-1.
5. Chang XL, Wang L, Guan SP, Kennedy BK, Liu JJ, Khor CC, et al. The association of genetically determined serum glycine with cardiovascular risk in East Asians. Nutr Metab Cardiovasc Dis 2021;31(6):1840 – 4. https://doi.org/10.1016/j.numecd.2021.03.010.
6. Jia Q, Han Y, Huang P, Woodward NC, Gukasyan J, Kettunen J, et al. Genetic determinants of circulating glycine levels and risk of coronary artery disease. J Am Heart Assoc 2019;8(10):e011922. https://doi.org/10.1161/JAHA.119.011922.
7. Burgess S, Davey Smith G, Davies NM, Dudbridge F, Gill D, Glymour MM, et al. Guidelines for performing Mendelian randomization investigations: update for summer 2023. Wellcome Open Res 2019;4:186. https://doi.org/10.12688/wellcomeopenres.15555.1.
8. Bowden J, Smith GD, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44(2):512 – 25. https://doi.org/10.1093/ije/dyv080.
9. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40(4):304 – 14. https://doi.org/10.1002/gepi.21965.
10. Del Greco MF, Minelli C, Sheehan NA, Thompson JR. Detecting pleiotropy in Mendelian randomisation studies with summary data and a continuous outcome. Stat Med 2015;34(21):2926 – 40. https://doi.org/10.1002/sim.6522.
11. Stamler J, Brown IJ, Daviglus ML, Chan Q, Miura K, Okuda N, et al. Dietary glycine and blood pressure: the international study on macro/micronutrients and blood pressure. Am J Clin Nutr 2013;98(1):136 – 45. https://doi.org/10.3945/ajcn.112.043000.
12. Slomowitz LA, Gabbai FB, Khang SJ, Satriano J, Thareau S, Deng AH, et al. Protein intake regulates the vasodilatory function of the kidney and NMDA receptor expression. Am J Physiol Regul Integr Comp Physiol 2004;287(5):R1184 – 9. https://doi.org/10.1152/ajpregu.00169.2003.
13. Ding YP, Svingen GFT, Pedersen ER, Gregory JF, Ueland PM, Tell GS, et al. Plasma glycine and risk of acute myocardial infarction in patients with suspected stable angina pectoris. J Am Heart Assoc 2015;5(1):e002621. https://doi.org/10.1161/JAHA.115.002621.

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Description of GWAS summary-level data used in this study.

Trait	Year	GWAS ID	Population	Sample size	Number of SNPs	Source (Pubmed ID)
Circulating glycine levels	2020	met-d-Gly	European	114,972	12,321,875	Nightingale Health Plc; Biomarker Quantification Version 2020
CAD	2015	ebi-a-GCST003116	European	141,217	8,597,751	26343387
CAD	2020	bbj-a-159	East Asian	212,453	8,881,048	–
BMI	2018	ieu-b-40	European	681,275	2,336,260	30124842
WHRadjBMI	2015	ieu-a-79	European	210,082	210,082	25673412
FG	2012	ebi-a-GCST005186	European	58,074	2,599,409	22581228
FI	2012	ebi-a-GCST005185	European	51,750	2,598,774	22581228
DBP	2018	ieu-b-39	European	757,601	7,160,619	30224653
SBP	2018	ieu-b-38	European	757,601	7,088,083	30224653
CRP	2018	ieu-b-35	European	204,402	2,414,379	30388399
IL-6	2019	prot-c-4673_13_2	European	1,338	501,428	28240269
TG	2013	ebi-a-GCST002216	European	94,595	2,410,057	24097068
TC	2013	ebi-a-GCST002221	European	94,595	2,418,562	24097068

Note: "–" means not applicable. ID means GWAS ID on the MRbase website, which is a website of large-scale public GWAS datasets; PMID, the ID number of the articles published in PubMed.

Abbreviation: SNP=single nucleotide polymorphism; GWAS=genome-wideassociation studies; CAD=coronary artery disease; BMI=body mass index; WHRadjBMI=waist-to-hip ratio adjusted for BMI; FG=fasting blood glucose; FI=fasting blood insulin; DBP=diastolic blood pressure; SBP=systolic blood pressure; IL-6=interleukin-6; CRP=C-reactive protein; TG=triglycerides; TC=total cholesterol.

SUPPLEMENTARY TABLE S2. Selection of valid genetic instruments based on UKB and Wittemans's study.

UKB									
SNP	**Chr**	**Pos**	**EA**	**NEA**	**EAF**	**β**	**Se**	***P***	**Loci**
rs10190808*,†	2	211993631	C	G	0.136421	0.0346173	0.0056719	2.40×10^{-9}	*CPS1-IT1*
rs10934753*,†	3	125906179	A	G	0.417116	0.0690031	0.0039623	3.40×10^{-74}	*ALDH1L1*
rs11045886	12	21386493	C	A	0.165117	0.0306817	0.0052791	8.30×10^{-9}	*SLCO1B1*
rs11172190	12	57766305	T	C	0.503709	0.0236924	0.0039114	1.00×10^{-10}	*R3HDM2*
rs112247225†	16	81154900	T	C	0.046621	−0.128232	0.0092851	5.20×10^{-45}	*PKD1L2*
rs11242109	5	131677047	T	G	0.47905	0.0226052	0.003901	2.00×10^{-8}	*SLC22A4*
rs149181595	15	43685807	C	A	0.027601	0.0942587	0.0119122	3.90×10^{-17}	*TUBGCP4*
rs17722201	2	209645912	C	T	0.219135	0.0275746	0.0047091	9.80×10^{-9}	*PTH2R*
rs192322963†	8	17445955	A	G	0.025449	0.0829439	0.0125376	4.10×10^{-11}	*PDGFRL*
rs1965869†	4	89677537	C	T	0.715726	−0.0242087	0.0043317	9.00×10^{-9}	*FAM13A*
rs2026972*,†	9	6538279	C	G	0.308331	−0.0821551	0.0042321	2.20×10^{-87}	*GLDC*
rs2608913†	6	131870261	C	T	0.217028	−0.0243496	0.0047367	2.30×10^{-8}	*ARG1*
rs2657879†	12	56865338	G	A	0.182536	0.0478885	0.0050385	5.20×10^{-22}	*GLS2*
rs2711697†	12	47265729	C	A	0.369926	0.0265213	0.0040341	1.10×10^{-11}	*SLC38A4*
rs28435239	9	5989087	A	G	0.769224	−0.0289595	0.0046491	8.60×10^{-10}	*KIAA2026*
rs34945403†	15	58430763	G	A	0.067631	−0.0634669	0.0080365	1.70×10^{-15}	*AQP9*
rs35034344†	2	211026796	T	A	0.273031	−0.0653462	0.0045911	1.90×10^{-46}	*KANSL1L*
rs4380169	2	212145768	C	T	0.490602	−0.0421118	0.0038951	3.60×10^{-27}	*ENSAP3*
rs4889229	16	81113672	T	C	0.917408	0.117726	0.0071008	4.20×10^{-64}	*RP11-303E16.10*
rs561931*,†	1	120254506	G	A	0.580975	0.0290991	0.0039588	4.50×10^{-14}	*PHGDH*
rs56819961†	12	47137673	C	T	0.212573	0.0426129	0.0047614	1.40×10^{-20}	*SLC38A4*
rs6587644	1	151994458	A	G	0.304982	0.0221024	0.0042589	2.40×10^{-8}	*NBPF18P*
rs67523949	12	348506	T	C	0.536231	0.0263338	0.0039096	3.30×10^{-11}	*SLC6A13*
rs7188156	16	79938114	G	T	0.14474	0.0317192	0.0055593	1.20×10^{-8}	*LINC01228*
rs75604103†	2	211692010	G	A	0.121625	−0.0989874	0.0060071	1.10×10^{-60}	*ENSAP3*
rs7704653†	5	90255685	G	A	0.724033	−0.0316456	0.0044087	3.70×10^{-13}	*ADGRV1*
rs7800001†	7	56072010	C	T	0.755284	0.0723549	0.0045524	5.50×10^{-61}	*GBAS*
rs79687284†	1	214150821	C	G	0.034645	0.0679817	0.0106777	7.80×10^{-11}	*PROX1-AS1*
rs9532939†	13	42440496	A	T	0.345473	0.0252027	0.0042637	8.70×10^{-9}	*VWA8*
rs11666281	19	18234588	T	C	0.25424	0.0044789	−0.0370833	1.30×10^{-17}	*MAST3*
rs6601302†	8	9239458	G	T	0.750342	0.004516	0.0276846	2.10×10^{-10}	–
rs2657879†	12	56865338	G	A	0.182536	0.0050385	0.0478885	5.20×10^{-22}	*GLS2*
rs28601761†	8	126500031	G	C	0.420161	0.003998	0.060914	1.40×10^{-55}	*TRIB1*
rs4240624	8	9184231	A	G	0.90923	0.0067925	−0.126861	2.00×10^{-82}	*LOC157273*
Wittemans's study									
rs4646961	1	76217169	A	G	0.297	0.048	0.006	8.41×10^{-19}	intronic variant in ACADM
rs561931*,†	1	120254506	G	A	0.593	0.033	0.006	7.57×10^{-14}	5' UTR variant of PHGDH
rs10184004†	2	165508389	T	C	0.4	0.036	0.006	1.53×10^{-9}	Intergenic variant near COBLL1 (28 kb) and GRB14 (30 kb)
rs715*,†	2	211543055	C	T	0.313	0.444	0.006	3.00×10^{-1632}	3'UTR variant of CPS1
rs9862438*	3	125910381	T	C	0.416	0.058	0.006	1.13×10^{-30}	ncRNA intronic variant in ALDH1L1-AS2

Continued

UKB									
SNP	**Chr**	**Pos**	**EA**	**NEA**	**EAF**	***β***	**Se**	***P***	**Loci**
rs148685782	4	155533035	G	C	0.996	0.309	0.049	2.01×10^{-10}	Synonymous variant in FGG
rs71640034	4	187161048	A	G	0.511	0.034	0.006	5.57×10^{-8}	intronic variant in KLKB1
rs156380	5	53378450	C	T	0.807	0.031	0.007	4.50×10^{-8}	intronic variant in ARL15
rs3105793	5	90226061	A	G	0.273	0.028	0.006	4.04×10^{-8}	intronic variant in ADGRV1
rs10900807	5	131757480	G	C	0.805	0.036	0.007	1.26×10^{-9}	ncRNA intronic variant in C5orf56
rs2545801	5	176841339	C	T	0.747	0.042	0.007	7.23×10^{-14}	intergenic variant near F12 (5 kb) and GRK6 (12 kb)
rs543159	6	160776017	A	C	0.482	0.035	0.006	4.20×10^{-10}	intronic variant in SLC22A3
rs4947534*	7	56079094	C	T	0.76	0.072	0.007	7.12×10^{-34}	3' UTR variant of PSPH
rs9987289†	8	9183358	A	G	0.1	0.124	0.01	1.74×10^{-49}	ncRNA intronic variant in LOC157273
rs28601761†	8	126500031	G	C	0.416	0.063	0.006	8.49×10^{-30}	intergenic variant near TRIB1 (49kb) and LINC00861 (435 kb)
rs17591030*	9	6550024	C	T	0.715	0.08	0.006	1.88×10^{-40}	intron variant in GLDC
rs676996†	9	136146077	T	G	0.668	0.04	0.006	4.39×10^{-15}	intron variant in ABO
rs190595610	10	32274880	A	G	0.997	0.253	0.056	8.96×10^{-9}	Intergenic variant near ARHGAP12 (57 kb) and KIF5B (23 kb)
rs10740134†	10	65315433	T	C	0.515	0.038	0.006	1.18×10^{-12}	intron variant in REEP3
rs12297321	12	47109387	T	C	0.152	0.048	0.008	7.41×10^{-13}	Intergenic variant near SLC38A4 (38 kb) and LOC100288798 (630 kb)
rs2638314	12	56866334	A	T	0.182	0.042	0.007	1.52×10^{-8}	intronic variant in GLS2
rs9514191	13	104520138	C	G	0.312	0.034	0.006	3.10×10^{-8}	intergenic variant near LINC01309 (440 kb) and DAOA-AS1(159 kb)
rs201393666	15	43677979	A	C	0.029	0.097	0.017	2.64×10^{-8}	intronic variant in TUBGCP4
rs2280195	15	58467095	A	G	0.441	0.028	0.006	3.15×10^{-9}	intronic variant in AQP9
rs9923732*	16	81110903	A	G	0.914	0.119	0.011	1.22×10^{-41}	Upstream variant of C16orf46, 9 kb downstream of GCSH
rs8078686†	17	45735706	C	T	0.509	0.035	0.006	3.66×10^{-11}	intron variant in KPNB1
rs273510†	19	18223350	A	G	0.708	0.034	0.006	3.57×10^{-9}	intron variant in MAST3

Note: "–" means Gene loci was not found. We excluded rs1047891 (homocysteine levels), rs11666281 (body mass index), rs13107325 (diastolic blood pressure), rs1801133 (homocysteine levels), rs2657879 (fasting blood glucose), rs28601761 (triglycerides), rs36105243 (type 2 diabetes), rs4240624 (total cholesterol), rs56113850 (smoking status: current), rs6601302 (body mass index), and rs79687284 (diabetes diagnosed by doctors) for pleiotropic effects (from PhenoScanner).

Abbreviation: UKB=UK Biobank; Chr=chromosome; Pos=position; EA=equal alleles; NEA=non-equal alleles; EAF=equal allele frequencies; Se=standard error; SNP=single nucleotide polymorphism; PSPH=phosphoserine phosphatase; GLDC=glycine decarboxylase; GCSH=glycine cleavage system protein H.

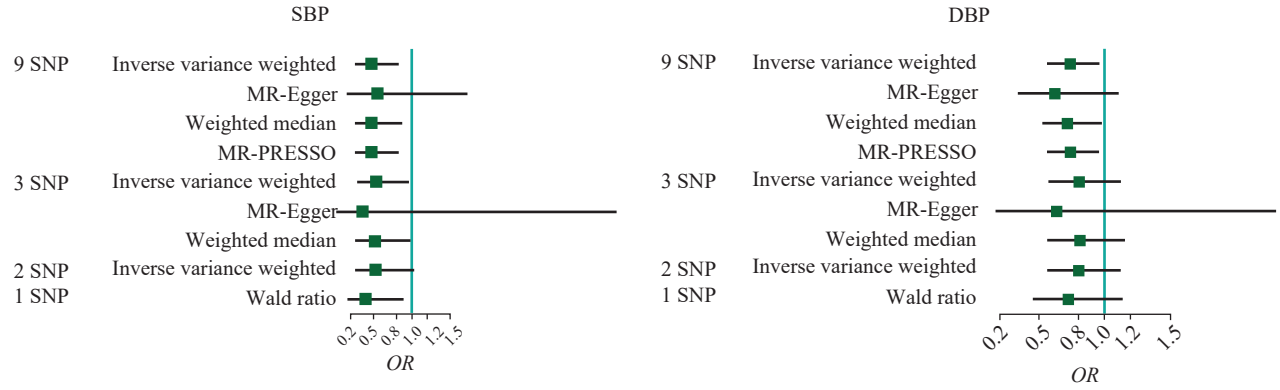
* means loci related to circulating glycine.

† means the SNPs used in this study.

SUPPLEMENTARY TABLE S3. The mediation effect of circulating glycine on CAD via SBP.

Mediator	**Total effect**	**Direct effect A**	**Direct effect B**	**Mediation effect**		**Mediated proportion (%)**
	***β* (95% *CI*)**	***β* (95% *CI*)**	***β* (95% *CI*)**	***β* (95% *CI*)**	***P***	**(95% *CI*)**
SBP	−0.20 (−0.34, −0.05)	−0.74 (−1.28, −0.20)	0.03 (0.02, 0.03)	-0.02 (-0.04, -4.94×10^{-3})	9.93×10^{-3}	6.06 (3.62, 10.64)

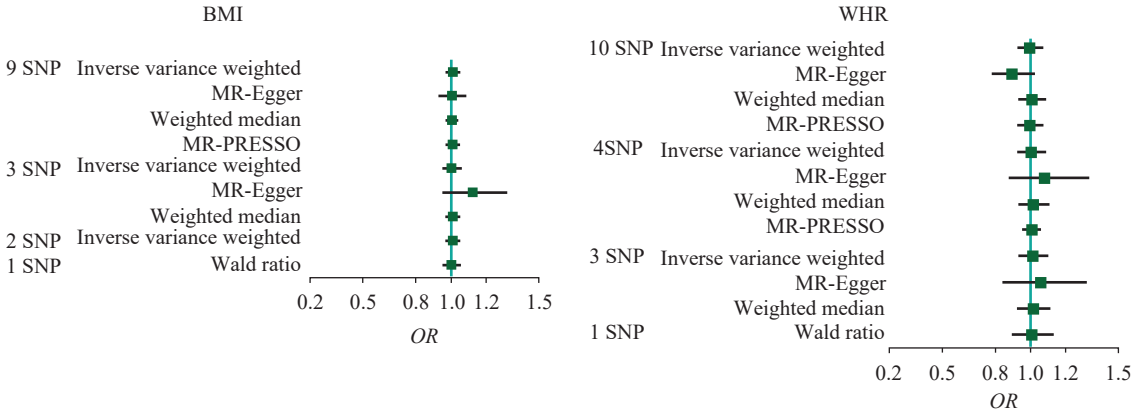
Abbreviation: *CI*=confidence interval; CAD=coronary artery disease; SBP=systolic blood pressure.



SUPPLEMENTARY FIGURE S1. Forest plots of the effect sizes ± 95% confidence intervals of the association between genetically predicted circulating glycine levels and SBP/DBP.

Note: The association effect size was estimated based on one standard deviation change of genetically predicted circulating glycine levels (9 SNP: in 19 SNPs,16 SNPs were available for SBP dataset; 1 SNP was palindromic with intermediate allele frequencies, and 6 SNPs were outliers removed by MR-PRESSO outlier test; 3 SNP: in 4 SNPs, 3 SNPs were available for SBP dataset; 2 SNP: in 3 SNPs, 2 SNPs were available for SBP dataset; 1 SNP: 1 SNP was available for SBP dataset; 9 SNP: in 19 SNPS,16 SNPs were available for DBP dataset; 1 SNP was palindromic with intermediate allele frequencies, and 6 SNPs were outliers removed by MR-PRESSO outlier test; 3 SNP: in 5 SNPs, 3 SNPs were available for DBP dataset; 2 SNP: in 3 SNPs, 2 SNPs were available for DBP dataset; 1 SNP: 1 SNP was available for DBP dataset).

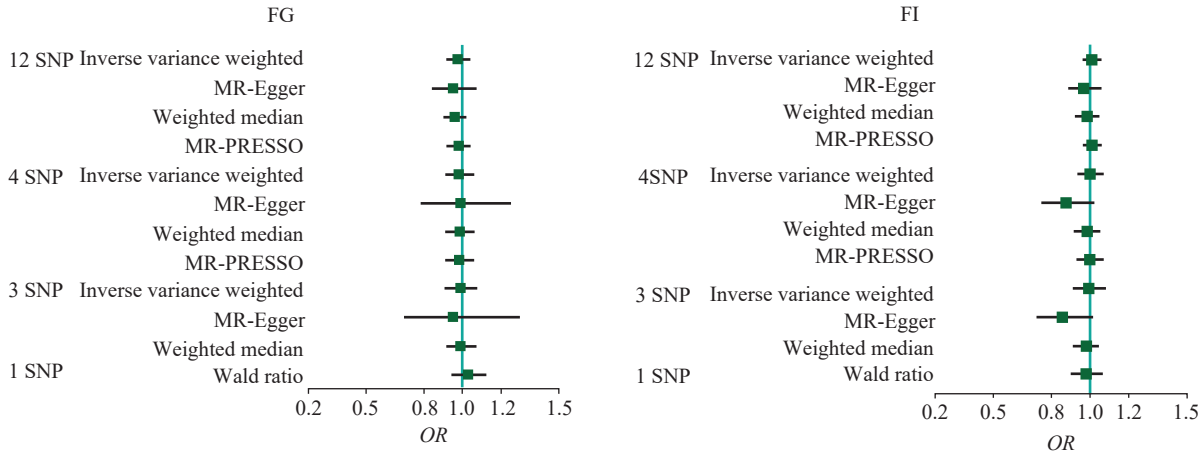
Abbreviation: MR-PRESSO=Mendelian Randomization Pleiotropy RESidual Sum and Outlier; SNP=single nucleotide polymorphism; DBP=diastolic blood pressure; SBP=systolic blood pressure.



SUPPLEMENTARY FIGURE S2. Forest plots of the effect sizes ± 95% confidence intervals of the association between genetically predicted circulating glycine levels and BMI/WHR.

Note: The association effect size was estimated based on one standard deviation change of genetically predicted circulating glycine levels (9 SNP: in 19 SNPs, 12 SNPs were available for BMI dataset, and 3 SNPs were outliers removed by MR-PRESSO outlier test; 3 SNP: in 4 SNPs, 3 SNPs were available for BMI dataset; 2 SNP: in 3 SNPs, 2 SNPs were available for BMI dataset; 1 SNP: 1 SNP was available for BMI dataset; 10 SNP: in 19 SNPs, 14 SNPs were available for WHR dataset, and 4 SNPs were outliers removed by MR-PRESSO outlier test; 4 SNP: 4 SNPs were available for WHR dataset; 3 SNP: 3 SNPs were available for WHR dataset; 1 SNP: 1 SNP was available for WHR dataset).

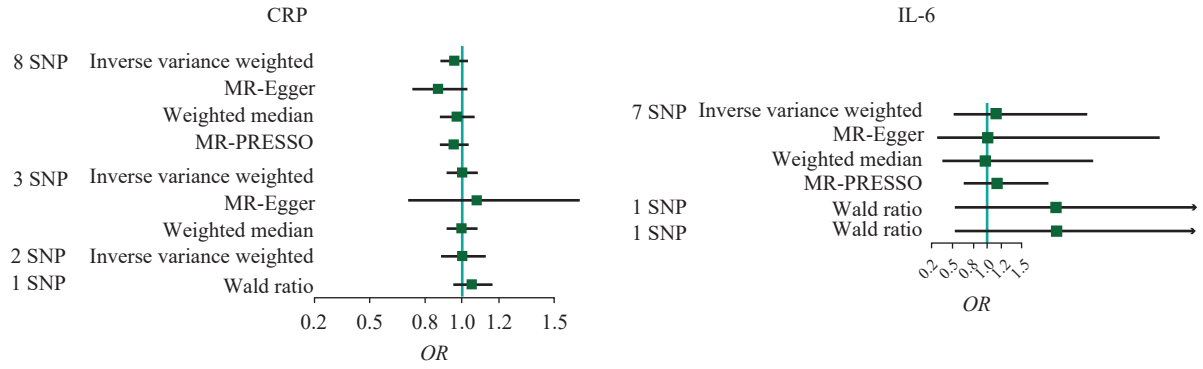
Abbreviation: SNP=single nucleotide polymorphism; MR-PRESSO=Mendelian Randomization Pleiotropy RESidual Sum and Outlier; BMI=body mass index; WHR=waist-to-hip ratio adjusted for body mass index.



SUPPLEMENTARY FIGURE S3. Forest plots of the effect sizes ± 95% confidence intervals of the association between genetically predicted circulating glycine levels and FG/FI.

Note: The association effect size was estimated based on one standard deviation change of genetically predicted circulating glycine levels (12 SNP: in 19 SNPs,14 SNPs were available for FG dataset, and 2 SNPs were outliers removed by MR-PRESSO outlier test; 4 SNP: 4 SNPs were available for FG dataset; 3 SNP: 3 SNPs were available for FG dataset; 1 SNP: 1 SNP was available for FG dataset; 12 SNP: in 19 SNPS,14 SNPs were available for FI dataset, and 2 SNPs were outliers removed by MR-PRESSO outlier test; 4 SNP: 4 SNPs were available for FI dataset; 3 SNP: 3 SNPs were available for FI dataset; 1 SNP: 1 SNP was available for FI dataset).

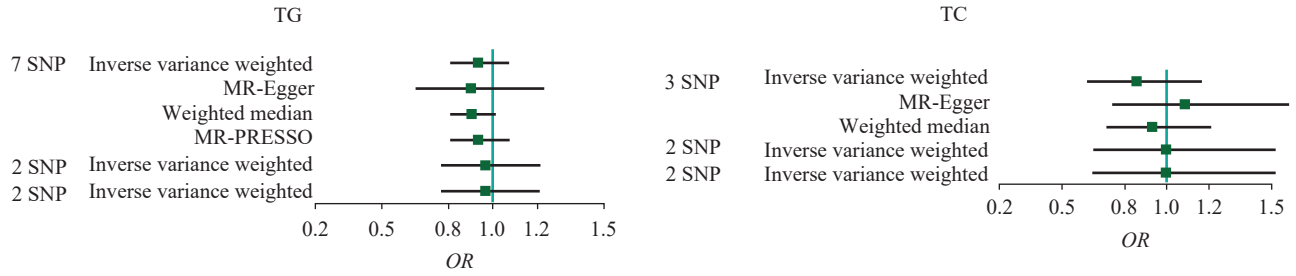
Abbreviation: SNP=single nucleotide polymorphism; MR-PRESSO=Mendelian Randomization Pleiotropy RESidual Sum and Outlier; FG=fasting blood glucose; FI=fasting blood insulin.



SUPPLEMENTARY FIGURE S4. Forest plots of the effect sizes ± 95% confidence intervals of the association between genetically predicted circulating glycine levels and CRP/IL-6.

Note: The association effect size was estimated based on one standard deviation change of genetically predicted circulating glycine levels (8 SNP: in 19 SNPS,13 SNPs were available for CRP dataset; and 5 SNPs were outliers removed by MR-PRESSO outlier test; 3 SNP: in 4 SNPs, 3 SNPs were available for CRP dataset; 2 SNP: in 3 SNPs, 2 SNPs were available for CRP dataset; 1 SNP: 1 SNP was available for CRP dataset. 7 SNP: in 19 SNPs, 8 SNPs were available for IL-6 dataset and 1 SNP was removed for being palindromic with intermediate allele frequencies; 1 SNP: in 4 SNPs, 2 SNPs were available for IL-6 dataset, and 1 SNP was removed for being palindromic with intermediate allele frequencies; 1 SNP: in 3 SNPS1 SNP was available for IL-6 dataset; 1SNP: 1 SNP was removed for being palindromic with intermediate allele frequencies).

Abbreviation: SNP=single nucleotide polymorphism; MR-PRESSO=Mendelian Randomization Pleiotropy RESidual Sum and Outlier; CRP=C-reactive protein; IL-6=Interleukin-6.



SUPPLEMENTARY FIGURE S5. Forest plots of the effect sizes ± 95% confidence intervals of the association between genetically predicted circulating glycine levels and TG/TC.

Note: The association effect size was estimated based on one standard deviation change of genetically predicted circulating glycine levels (7 SNP: in 19 SNPS 14 SNPs were available for TG dataset, 2 SNPs were removed for being palindromic with intermediate allele frequencies, and 5 SNPs were outliers removing by MR-PRESSO outlier test; 2 SNP: in 4 SNPs, 4 SNPs were available for TG dataset, 2 SNPs were removed for being palindromic with intermediate allele frequencies; 2 SNP: in 3 SNPS, 1 SNP was removed for being palindromic with intermediate allele frequencies 1 SNP: was removed for being palindromic with intermediate allele frequencies. 3 SNP: in 19 SNPs, 14 SNPs were available for TC dataset 2 SNPs were removed for being palindromic with intermediate allele frequencies, and 9 SNPs were outliers removing by MR-PRESSO outlier test; 2 SNP: in 4 SNPs, 4 SNPs were available for TC dataset, 2 SNPs were removed for being palindromic with intermediate allele frequencies; 2 SNP: in 3 SNPs, 1 SNP was removed for being palindromic with intermediate allele frequencies; 1 SNP: was removed for being palindromic with intermediate allele frequencies).

Abbreviation: SNP=single nucleotide polymorphism; MR-PRESSO=Mendelian Randomization Pleiotropy RESidual Sum and Outlier; TG=Triglyceride; TC=Total cholesterol.

Youth Editorial Board

Indexed by Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), PubMed Central (PMC), Scopus, Chinese Scientific and Technical Papers and Citations, and Chinese Science Citation Database (CSCD)

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 6 No. 9 Mar. 1, 2024

Responsible Authority
National Disease Control and Prevention Administration

Sponsor
Chinese Center for Disease Control and Prevention

Editing and Publishing
China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN
ISSN 2096-7071
CN 10-1629/R1