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

CHINA CDC WEEKLY

Vol. 5 No. 44 Nov. 3, 2023

中国疾病预防控制中心周报

ISSN 2096-7071

China CDC Weekly

Cover Image: adapted from the World Health Organization, https://www.who.int/multi-media/details/vector-borne-diseases-infographic.

Preplanned Studies

Impact of HIV/HCV Co-Infection on Mortality and Attrition in Antiretroviral Therapy Among People with HIV — Guangxi Zhuang Autonomous Region, China, 2003–2022

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Summary

What is already known about this topic?

The effects of concurrent human immunodeficiency virus (HIV)/hepatitis C virus (HCV) infection on mortality and patient attrition in those undergoing antiretroviral therapy continue to be a contested area of research.

What is added by this report?

According to the propensity score-matched cohort, individuals with HIV/HCV co-infection exhibit an elevated risk of all-cause mortality [adjusted hazard ratio: 2.048, 95% confidence interval (*CI*): 1.526–2.749] and attrition (adjusted incidence rate ratio: 1.659, 95% *CI*: 1.4.8–1.961) compared to their counterparts who are mono-infected with HIV.

What are the implications for public health practice?

The pressing need for tailored testing and follow-up protocols for individuals co-infected with HIV/HCV cannot be overstated.

In the current era of antiretroviral therapy (ART), effective management of patients coinfected with human immunodeficiency virus (HIV)/hepatitis C virus (HCV) is increasingly critical in reducing mortality rates (*1*). Attrition, defined as loss to patient follow-up or discontinuation of ART, is not merely an indicator for evaluating treatment adherence but also a pivotal factor for effectively managing patients on long-term ART (*2*). However, the influence of HIV/HCV coinfection on mortality and attrition is still a matter of ongoing debate (*3*).

In the Guangxi Zhuang Autonomous Region, an estimated 6.6% of individuals undergoing ART were identified as coinfected with HCV (*4*). This sizeable percentage of HIV/HCV coinfected patients presents unprecedented challenges to the implementation of ART in Guangxi. Prior non-matching studies indicated that most individuals contracted HIV/HCV coinfections through intravenous drug use, while HIV mono-infections were primarily acquired through heterosexual contacts (*3–4*). However, differences in population composition between these groups might introduce a selection bias. Thus, establishing a recent basis for evaluation is vital for planning effective management strategies.

Findings from the analysis of the propensity score-matched (PSM) cohort, abstracted from China's National Free Antiretroviral Treatment Program database, showed that HIV/HCV coinfected individuals faced an enhanced risk of all-cause mortality and ART attrition compared to those exclusively infected with HIV. These insights may provide crucial inputs in constructing personalized testing and follow-up protocols for HIV/HCV coinfected patients undergoing ART.

We amassed clinical data from individuals who commenced ART across all 109 allocated hospitals within the 14 prefectures of Guangxi from December 2003 to December 2022. To be qualified for inclusion in the study, participants must have been aged 15 years or older at the time of commencing ART, have had no prior ART experience, and have initiated a standard three-drug regimen in China. Exclusions were made for individuals without the necessary baseline characteristics and initial testing records required for this study, those lacking any follow-up records or drug supply records at the first follow-up appointment, individuals who tested positive for hepatitis B virus (HBV) surface antigen at ART's initiation, and those lacking $CD4^+$ T-lymphocyte (CD4) count and HIV viral load records in the first and second follow-up years.

Eligible individuals were categorized into two groups according to PSM, specifically those co-infected with HIV/HCV and those solely infected with HIV (Supplementary Figure S1, available in https://weekly.chinacdc.cn/). Those testing negative for HCV

antibody and HBV surface antigen were classified as HIV mono-infections, and those testing positive for HCV antibody and negative for HBV surface antigen are categorized as HIV/HCV co-infections. Sex, age, CD4 count, route of HIV infection, primary regimen, and extent of liver damage were chosen as the determining variables. This study employed nearest neighbor matching methods, a seed of 1,234, and a caliper of 0.0001 to match propensity scores.

The initial testing was identified as the last test within three months prior to the ART commencement. Survival time was interpreted as the period from the commencement of ART to death from any cause. Individuals were considered censored when their fate was unknown due to either loss to follow-up or discontinuation of ART, or by December 31, 2022. After ART's initiation, HIV viral load and CD4 count were closely monitored once every 12 months. For mortality analysis, we used a survival curve to indicate the discrepancy in survival probabilities between the two groups, and a Cox proportional hazard model to compute the adjusted hazard ratio (a*HR*). For attrition analysis, a bee-swarm plot visualized the years from the ART initiation to the first recorded attrition, and the adjusted incidence rate ratio (a*IRR*) was calculated using a Poisson regression model.

Considering that group matching with PSM is not unique and one individual may be matched to others without significantly altering the association, pair analysis was excluded from this study. In order to pinpoint risk within different subsets of the population, multivariable analyses were broken down by initial liver impairment grade. All statistical analyses were conducted on R (version 4.2.0; R Foundation for Statistical Computing), with tests being 2-sided, and *P* values of less than 0.05 deemed statistically significant.

Our analyses included 1,191 individuals mono-infected with HIV and an equal number of individuals

TABLE 1. Baseline characteristics of individuals co-infected with HIV/HCV and mono-infected with HIV in antiretroviral therapy in Guangxi, China, 2003–2022.

Characteristics	Overall (*N*=2,382)	HIV (*N*=1,191)	HIV/HCV (*N*=1,191)	Test statistic	*P*
Sex, *n* (%)				0 (χ^2)	1.000
Male	1,624 (68.2)	812 (68.2)	812 (68.2)		
Female	758 (31.8)	379 (31.8)	379 (31.8)		
Age [years, mean (standard deviation)]	41.1 (12.0)	41.3 (11.1)	41.2 (11.5)	−0.486 (*t*)	0.627
CD4 count [cells/μL, median (interquartile range)]	174 (46–302)	170 (38–309)	178 (56–293)	692,032 (*w*)	0.305
Route of HIV infection, *n* (%)				0 (χ^2)	1.000
Injecting drug use	98 (4.1)	49 (4.1)	49 (4.1)		
Heterosexual contact	2,240 (94.0)	1,120 (94.0)	1,120 (94.0)		
Homosexual contact with men	44 (1.8)	22 (1.8)	22 (1.8)		
Primary regimen, *n* (%)				0.940 (χ^2)	0.332
NNRTI backbone	2,186 (91.8)	1,100 (92.4)	1,086 (91.2)		
PI or INSTI backbone	196 (8.2)	91 (7.6)	105 (8.8)		
Hepatic impairment, *n* (%)				0.817 (χ^2)	0.665
Normal	488 (20.5)	252 (21.2)	236 (19.8)		
Grade 1/2	1,216 (51.0)	607 (51.0)	609 (51.1)		
Grade 3/4	678 (28.5)	332 (27.9)	346 (29.1)		

Note: HIV refers to individuals mono-infected with HIV, while HIV/HCV denotes individuals co-infected with both HIV and HCV. The NNRTI backbone regimen incorporates two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor. The PI backbone regimen includes two nucleoside reverse transcriptase inhibitors and one protease inhibitor, while the INSTI backbone regimen contains two nucleoside reverse transcriptase inhibitors and one integrase strand transfer inhibitor. As per the China Free Antiretroviral Therapy Manual, the upper limit of normal (ULN) for aspartate transaminase (AST), alanine aminotransferase (ALT), and total bilirubin (TBIL) is set at 40 U/L, 40 U/L, and 23 μmol/L respectively. Hepatic impairment is graded as 1 (AST and/or ALT > 1-time ULN, TBIL > 1-time ULN), 2 (AST and/or ALT > 2.5-time ULN, TBIL > 1.5-time ULN), 3 (AST and/or ALT > 5-time ULN, TBIL > 2.5-time ULN), and 4 (AST and/or ALT > 10-time ULN, TBIL > 5-time ULN). Chi-squared test, T-test, and Wilcoxon test were respectively used to calculate the test statistics, denoted as χ^2, *t*, and *w*.

Abbreviation: CD4=CD4$^+$ T-lymphocyte; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INSTI=integrase strand transfer inhibitor.

co-infected with HIV/HCV. There were no significant differences in baseline characteristics between the two groups, as demonstrated in Table 1.

In our analysis of all-cause mortality, we observed that of the individuals solely infected with HIV, 68 were deceased. They collectively contributed to a person-time at risk of 8,717.11 person-years (PY), resulting in a mortality rate of 0.78/100 PY [95% confidence interval (*CI*): 0.62–0.99]. In contrast, among those co-infected with HIV/HCV, 135 individuals were deceased. They amounted to a person-time at risk of 8,767.24 PY, leading to an increased mortality rate of 1.54/100 PY (95% *CI*: 1.30–1.82). The survival probability notably declined more rapidly for both groups (Figure 1).

Comparing infection scenarios, co-infection with HIV/HCV consequently led to an augmented all-cause mortality risk by 104.8%, compared to individuals solely infected with HIV (a*HR*: 2.048, 95% *CI*: 1.526–2.749, *P*<0.001).

Within the cohort devoid of initial hepatic impairment, the risk of all-cause mortality remained similar for HIV/HCV co-infected individuals and those exclusively infected with HIV (a*HR*: 1.544, 95% *CI*: 0.748–3.188, *P*=0.240). However, when evaluating subgroups with initial grade 1/2 and grade 3/4 hepatic impairment, the disparity in all-cause mortality risk between HIV/HCV co-infected individuals and those only infected with HIV was pronounced (Grade 1/2: a*HR*: 2.008, 95% *CI*: 1.345–3.000, *P*=0.001; Grade 3/4: a*HR*: 2.511, 95% *CI*: 1.432–4.403, *P*=0.001) as presented in Table 2.

Higher attrition rates were found in individuals co-infected with HIV/HCV compared to individuals only infected with HIV (Figure 2). Despite this, the HIV/HCV co-infection group presented with a significantly extended median time from ART initiation to the first instance of attrition, as compared to the HIV-only group (Figure 2). Those co-infected with HIV/HCV were generally more prone to attrition (a*IRR*: 1.659, 95% *CI*: 1.408–1.961, *P*<0.001) when compared to those only infected with HIV. Similarly, those co-infected with HIV/HCV had an equivalent risk of attrition to the individuals only infected with HIV within subgroups without initial hepatic impairment (a*IRR*: 1.372, 95% *CI*: 0.938–2.018, *P*=0.105), and heightened attrition risk in subgroups exhibiting initial hepatic impairment grade 1/2 (a*IRR*: 1.806, 95% *CI*: 1.427–2.298, *P*<0.001) and grade 3/4 (a*IRR*: 1.860, 95% *CI*: 1.375–2.514, *P*<0.001) (Table 2).

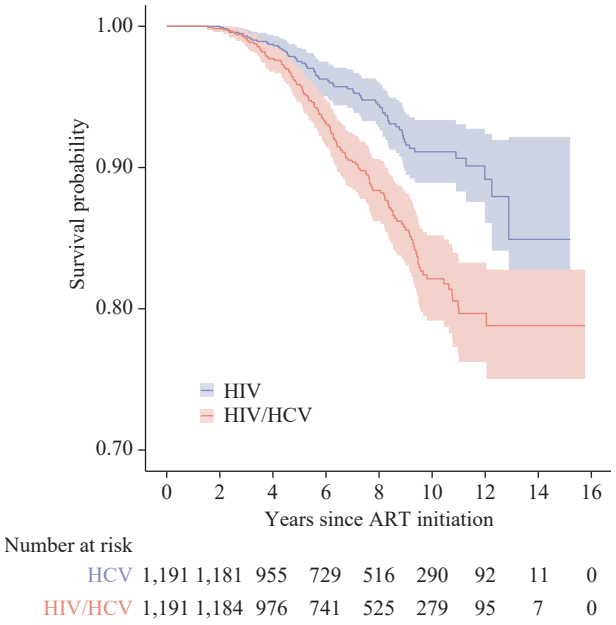

FIGURE 1. Comparison of survival probability at given years after antiretroviral therapy initiation between individuals co-infected with HIV/HCV and those mono-infected with HIV in Guangxi, China, 2003–2022.
Note: HIV denotes individuals mono-infected with human immunodeficiency virus, and HIV/HCV represents individuals co-infected with both human immunodeficiency virus and hepatitis C virus.
Abbreviation: ART=antiretroviral therapy.

DISCUSSION

The results of this study underscore that individuals co-infected with HIV/HCV in Guangxi face an elevated risk of all-cause mortality and ART attrition in comparison to their counterparts with only HIV mono-infection. These observations underscore earlier findings detailing shorter survival times in HIV/HCV co-infected individuals, even subsequent to ART (*3*–*5*). Further, initial hepatic impairment in individuals simultaneously infected with HIV/HCV corresponded with an increased risk of all-cause mortality.

While individuals co-infected with HIV/HCV exhibited higher attrition rates compared to their HIV mono-infected counterparts, the median duration from ART initiation to the first instance of attrition was notably extended in the co-infected group. This unexpected observation suggests the possible early implementation of intervention strategies for the co-infected population. However, these measures fail to prevent long-term ART interruption in individuals with concurrent HIV/HCV infection. Prior research has documented a correlative high risk of both

TABLE 2. The associations between HIV/HCV co-infection with all-cause mortality and attrition in antiretroviral therapy in Guangxi, China, 2003–2022.

Characteristics	All-cause mortality a*HR*	*P*	Attrition a*IRR*	*P*
Group*				
HIV	1		1	
HIV/HCV	2.048 (1.526–2.749)	<0.001	1.659 (1.408–1.961)	<0.001
Stratified by hepatic impairment†				
Normal				
HIV	1		1	
HIV/HCV	1.544 (0.748–3.188)	0.240	1.372 (0.938–2.018)	0.105
Grade 1/2				
HIV	1		1	
HIV/HCV	2.008 (1.345–3.000)	0.001	1.806 (1.427–2.298)	<0.001
Grade 3/4				
HIV	1		1	
HIV/HCV	2.511 (1.432–4.403)	0.001	1.860 (1.375–2.514)	<0.001

Note: HIV represents individuals mono-infected with HIV, whereas HIV/HCV refers to individuals co-infected with both HIV and HCV. a*HR* stands for the adjusted hazard ratio, determined by the Cox proportional hazard model. Meanwhile, a*IRR* denotes the adjusted incidence rate ratio obtained through the Poisson regression model. The attrition factor incorporates losses to follow-up along with discontinuation of antiretroviral therapy. Per the prescripts in the China Free Antiretroviral Therapy Manual, the upper limit of normality (ULN) for aspartate transaminase (AST), alanine aminotransferase (ALT), and total bilirubin (TBIL) are set at 40 U/L, 40 U/L, and 23 μmol/L, respectively. Hepatic impairment is categorized into four grades: grade 1 (AST and/or ALT > 1-time ULN, TBIL > 1-time ULN), grade 2 (AST and/or ALT > 2.5-time ULN, TBIL > 1.5-time ULN), grade 3 (AST and/or ALT > 5-time ULN, TBIL > 2.5-time ULN), and grade 4 (AST and/or ALT > 10-time ULN, TBIL > 5-time ULN).

* The models were adjusted for sex, age, initial CD4 count, route of HIV infection, the primary regimen type, and hepatic impairment grade.

† The models were adjusted for sex, age, initial CD4 count, route of HIV infection, and the primary regimen.

mortality and attrition amongst this demographic, particularly those who contract HIV/HCV through injecting drug use (*6*–*7*). Efforts to counteract this trend include the development of extended-release regimens and non-pharmacological interventions aimed at enhancing adherence (*8*–*9*). However, our research indicates that despite controlling for the HIV infection route and other initial characteristics, co-infected individuals consistently demonstrated a higher attrition propensity compared to those only afflicted with HIV. Moreover, stratified analyses highlighted hepatic impairment as a significant contributing factor for attrition within co-infected subgroups. This outcome suggests that prospective testing and follow-up protocols for co-infected patients need to incorporate baseline hepatic impairment assessment.

The present findings are not without their limitations. First, the high specificity of the matching criteria constrains the number of individuals included in the study, which could influence the results. Notwithstanding, attempts to enlarge the sample size by employing a 1∶2 and 1∶3 matching ratio posed further challenges. An increase in the count of individuals with HIV/HCV co-infection could not be proportionally matched with individuals presenting only HIV, thereby upsetting the equilibrium of baseline characteristics between the groups and augmenting the confounding effects. Given these constraints, a 1∶1 matching strategy might constitute an effective compromise. Second, the unavailability of data on HCV RNA and other variants of hepatitis viruses could potentially exaggerate the estimated impacts of chronic HCV infections, while downplaying the effects of concealed hepatitis virus infection. Third, we could not explore HIV- or HCV-related deaths due to the absence of data regarding the cause of death. Despite this, investigating the consequences of HIV/HCV co-infection on all-cause mortality in individuals on long-term ART can provide valuable insights for devising intervention strategies.

To our knowledge, this study is the first to explore the impact of HIV/HCV co-infection on prognostic outcomes in individuals receiving ART derived from a PSM cohort. The outcomes underscore the immediate necessity for tailored testing and follow-up plans for those co-infected with HIV/HCV, contingent upon their initial hepatic impairment classification (*10*).

Conflicts of interest: No conflicts of interest.

Funding: Supported by National Natural Science Foundation of China (12071366), the Guangxi Key

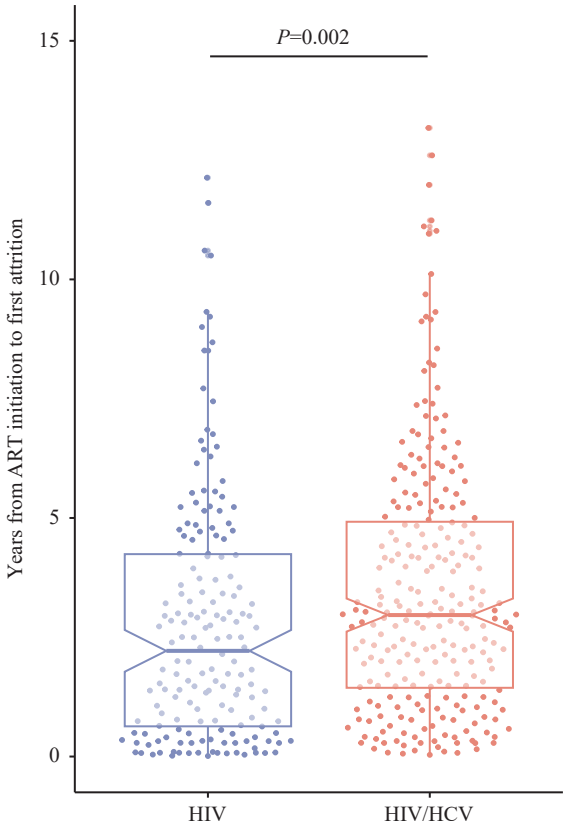

FIGURE 2. Comparison of attrition of antiretroviral therapy between individuals co-infected with HIV/HCV and those mono-infected with HIV.
Note: HIV column means individuals mono-infected with human immunodeficiency virus; HIV/HCV column means individuals co-infected with both human immunodeficiency virus and hepatitis C virus. The points represent years from ART initiation to the first attrition. The notches, upper edges, and lower edges of the boxes represent the median, first quartile, and third quartile of years from ART initiation to the first attrition, respectively.
Abbreviation: ART=antiretroviral therapy.

Laboratory of AIDS Prevention Control and Translation of Guangxi Zhuang Autonomous Region (ZZH2020010), and the Guangxi Bagui Scholars Program of Key Technical Position for HIV/AIDS Prevention and Control.

doi: 10.46234/ccdcw2023.183

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Submitted: July 07, 2023; Accepted: October 23, 2023

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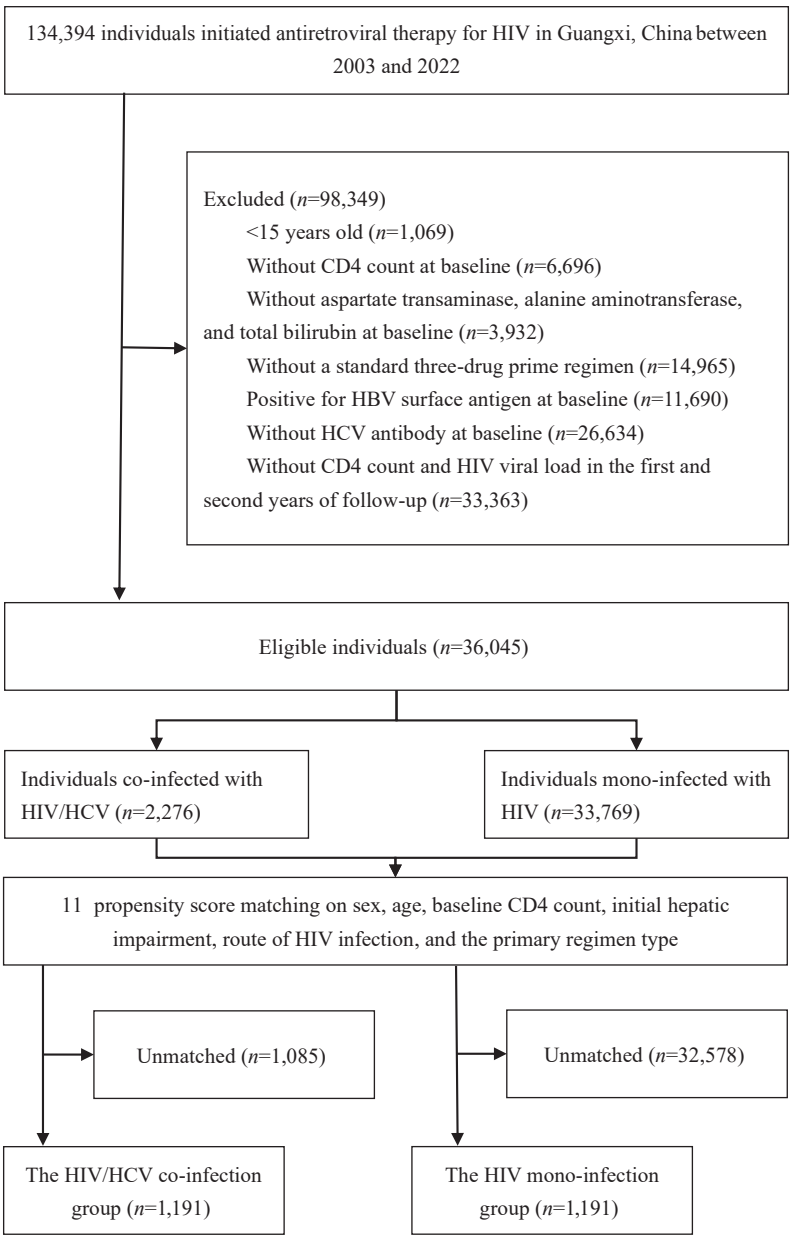
SUPPLEMENTARY MATERIALS



SUPPLEMENTARY FIGURE S1. Study flow chart of individual screening, enrollment, matching — Guangxi, China, 2003–2022.

Note: HIV refers to human immunodeficiency virus, while HCV denotes hepatitis C virus. HBV signifies hepatitis B virus, and CD4 represents $CD4^+$ T-lymphocyte.

Preplanned Studies

Analyzing the Trends and Causes of Birth Defects — Jinan City, Shandong Province, China, 2005–2022

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Summary

What is already known about this topic?

Numerous studies conducted in China have reported on the prevalence of birth defects (BDs). However, the limited surveillance periods in select studies curtail comprehensive trends and cause evaluation. Accordingly, the surveillance duration of BDs is extended, and a comprehensive analysis of their prevailing trends is conducted to provide a basis for government intervention and policy implementation.

What is added by this report?

There is a distinct increase in the incidence of BDs observed in Jinan. In rural areas, a pronounced upward trend was observed, and the increase was more rapid than in urban areas. BD prevalence among mothers over 35 years old and under 20 years old was substantially higher than BD prevalence rates in other maternal age brackets. Specifically, the period from 2005 to 2022 saw the prevalence of congenital heart disease surge, the fastest average annual growth rate among all birth defects.

What are the implications for public health practice?

It's essential to prioritize pregnant women in rural areas and those at both ends of the maternal age spectrum. Implementing comprehensive initiatives is crucial to address the high prevalence of congenital heart disease.

Birth defects (BDs) are a collection of structural, functional, and/or biochemical-molecular anomalies identifiable at birth (*1*). With advancements in economic and social sectors, mortality rates from infections and malnutrition among children and adolescents have significantly decreased. However, there's a rising trend in deaths due to BDs (*2*). Current estimates suggest that BD prevalence is 4.7% in developed countries, 5.6% in middle-income countries, and 6.4% in low-income countries (*3*). Moreover, disabilities and cancer arising from birth defects pose growing threats to children's health (*4*). Given these developments, BDs have become a critical global health concern demanding urgent attention.

In this context, China has also seen a rise in the significance of BDs in public health. According to the 2012 "Birth Defect Prevention Report" published by the Ministry of Health, China's prevalence rate was 5.6 per 10,000 births in 2011 (*5*). Notably, 19.1% of infant deaths were attributable to BDs, and BDs were the root cause of 9.6% of disabilities. Furthermore, BDs were established as the second leading cause of infant death in China (*6*). Given its status as a developing nation with a large population, it is critical for China to reduce the incidence rates of birth defects.

Many Chinese studies have reported on the prevalence of BDs. Current protocols mandate reporting prenatal abnormalities in body structure, function, or metabolism. The extensive use of ultrasound technology in obstetrics has led to an increase in the detection of BDs prior to 28 weeks of gestation. Consequently, there is a compelling need to extend the surveillance period for birth defects.

In Jinan, most expectant mothers typically initiate hospital visits around the 12th week of gestation to secure a maternal record and undergo a medical examination. Therefore, starting birth defect monitoring from this gestational stage is both methodologically robust and practically feasible. As a result, a birth defect monitoring network was established across all district and county levels in Jinan in 2005. Accordingly, a birth defect monitoring network encompassing all district and county levels throughout Jinan was established in 2005. Health centers at the township level and county-level hospitals providing midwifery services were required to report relevant birth defect data. In 2011, the reach of this network was expanded to include all medical institutions offering pregnancy health and midwifery services. Additionally, an information system designed to collect precise birth defect data was implemented in the same year. All information relating to mothers and newborns, inclusive of data on birth defects, was submitted via an online reporting system, enabling accurate and reliable data.

Between 2005 and 2008, BDs were identified from the 28th week of gestation until 7 days post-birth. However, from 2008 to 2022, the period for determining BDs broadened to begin at 12 weeks gestation and extended through to 7 days after birth. Our study holds the potential to inform governmental policy-making with scientifically-based recommendations and serve as a template for developing cities to prevent BDs.

Data was aggregated from registry forms and an electronic information system. Between 2005 and 2015, paper forms were utilized for data collection. However, during 2015–2022, data compilation transitioned to an electronic information system. The collected data encompassed a range of factors such as the total number of births, maternal age, residency location (either urban or rural), and neonate gender. We accounted for 1,463,842 births and 28,537 BDs within our study.

Both external malformations and chromosomal aberrations, encompassed under BDs, were diagnosed under the International Classification of Diseases (10th edition).

To maintain data accuracy, standardized procedures were established for data handling, abstraction, and evaluation. Hospital surveillance teams verified diagnoses, reviewed data, and checked medical records following these standards. Annual surveys revealed a 0.5% underreporting rate of birth defects in Jinan. Missing reports were documented yearly.

The Cochran-Armitage test (CAT) was used to analyze the trends of BD prevalence. Differences in BDs were tested using the Chi-square test. All statistical analyses were executed using SPSS software (version 18.0: IBM Corp., Armonk, NY, USA), with a significance level of $P<0.05$.

Between 2005 and 2022, there were 1,463,842 recorded births and 28,537 instances of BDs, yielding a prevalence of 194.93 per 10,000 births. Time trend analysis illustrated a rise in BD rates from 99.15 per 10,000 births in 2005 to 290.27 per 10,000 births in 2022. This represents an aggregate increase of 191.21% and an annual increase of 10.70% ($P<0.05$). The peak birth defect prevalence was in 2022, at 290.27 per 10,000 births. A significant increase inflection point was identified in 2016, with prevalences exceeding 230 per 10,000 births from then on.

During the study period, urban areas had a BD rate of 234.54 per 10,000 births, while rural areas had 161.40 per 10,000 births. The prevalence in urban areas significantly surpassed that in rural areas, averaging 31.17% ($P<0.05$). A time trend analysis indicated an increase in the incidence of BDs in both urban and rural areas, with the average annual growth rate in rural environments being faster than in urban ones (13.63% *vs*. 7.85%) (Table 1 and Figure 1).

Throughout our study, we observed a significantly higher prevalence of BDs in two specified age groups. Mothers under 20 had a BD rate of 272.91 per 10,000 births, and those over 35 had 236.09 per 10,000 births. These age groups showed significantly higher BD incidences compared to other groups ($P<0.05$).

From 2005 to 2022, the proportion of pregnant women under 20 surged by 2037.50%, while those over 35 increased by 66.35% (Table 2).

From 2005 to 2022, the top 5 BDs were congenital heart disease (88.54 per 10,000 births), polydactyly (19.23 per 10,000 births), cleft lip and/or palate (10.41 per 10,000 births), hypospadias (9.84 per 10,000 births), and syndactyly (5.35 per 10,000 births).

Of the 10 major BDs analyzed, 7 showed an upward trend, and 3 declined from 2005 to 2022 ($P<0.05$). Congenital heart disease exhibited a significant increase at 867.36%, reflecting an average annual growth of 48.19%. The occurrence of Down syndrome similarly increased by 299.14%, with an average annual increase of 16.62%. Polydactyly also rose by 223.09%, averaging an annual increase of 12.39%. On the other hand, Neural Tube Defects demonstrated a stark decrease at 90.35%, with an average annual decline of 5.02%. The rates of Congenital Hydrocephalus similarly fell by 63.81%, with an average annual decrease of 3.54%. Limb Shortening also declined by 53.19%, averaging an annual decrease of 2.96%. (Table 3 and Figure 2).

DISCUSSION

The results indicated a prevalence rate of BDs in Jinan of 194.93 per 10,000 live births between 2005 and 2022. Furthermore, the prevalence of birth defects was observed to increase at an annual rate of 10.71%, surpassing the growth rates recorded in Jiangsu (*7*), Hunan (*8*), and Sichuan (*9*). This growing issue demands significant attention from relevant governmental sectors.

A significant shift in growth trends was identified in

TABLE 1. The prevalence of birth defects in Jinan from 2005 to 2020.

Year	Total*			Urban*			Rural*		
	Births	BDs	PRE	Births	BDs	PRE	Births	BDs	PRE
2005	47,302	469	99.15	19,467	255	130.99	27,835	214	76.88
2006	49,964	620	124.09	18,957	331	174.61	31,007	289	93.20
2007	60,206	627	104.14	25,154	375	149.08	35,052	252	71.89
2008	58,797	673	114.46	23,975	400	166.84	34,822	273	78.40
2009	66,767	690	103.34	26,603	376	141.34	40,164	314	78.18
2010	80,960	951	117.47	36,732	545	148.37	44,228	406	91.80
2011	81,422	1,431	175.75	36,700	819	223.16	44,722	612	136.85
2012	89,054	1,347	151.26	39,763	728	183.08	49,291	619	125.58
2013	77,458	1,156	149.24	35,551	600	168.77	41,907	556	132.67
2014	109,211	1,530	140.10	51,363	813	158.29	57,848	717	123.95
2015	76,440	1,420	185.77	35,959	762	211.91	40,481	658	162.55
2016	131,469	3,068	233.36	62,281	1,750	280.98	69,188	1,318	190.50
2017	102,681	2,781	270.84	49,217	1,589	322.86	53,464	1,192	222.95
2018	100,077	2,652	265.00	48,853	1,453	297.42	51,224	1,199	234.07
2019	102,254	2,718	265.81	49,126	1,500	305.34	53,128	1,218	229.26
2020	83,811	2,270	270.85	40,445	1,240	306.59	43,366	1,030	237.51
2021	73,594	2,039	276.31	36,136	1,100	304.41	37,658	939	249.35
2022	72,175	2,095	290.27	35,126	1,111	316.29	37,049	984	265.59
Total	1,463,842	28,537	194.93	671,408	15,747	234.54	792,434	12,790	161.40
AAGR			10.71			7.85			13.63

Abbreviation: BDs=birth defects; PRE=prevalence (per 10,000 births); CAT=Cochran-Armitage trend; AAGR=average annual growth rate.
* CAT $P<0.05$.

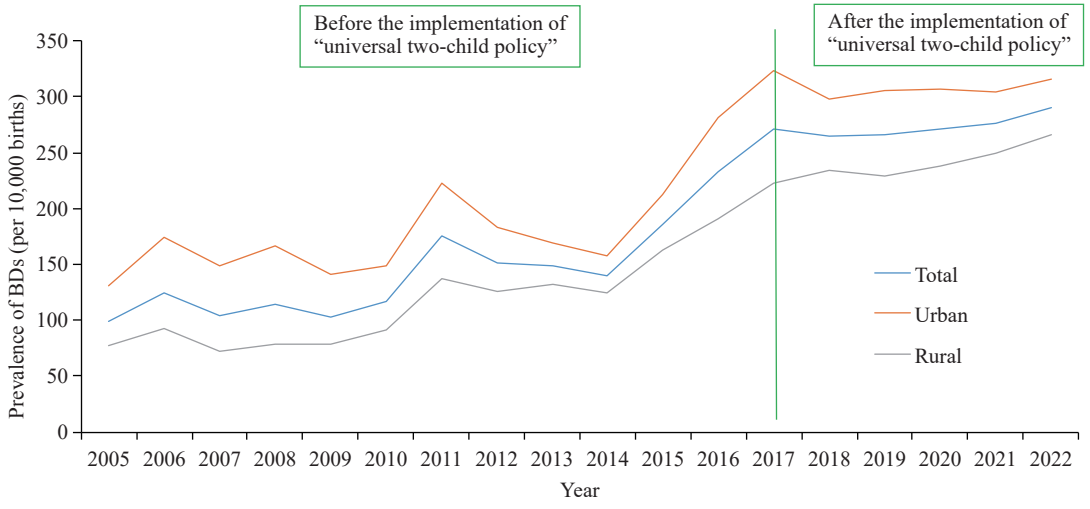

FIGURE 1. The prevalence of birth defects between urban areas and rural areas from 2005 to 2020.
Note: Two distinct periods were demarcated based on changes in population policies: 2005–2016, preceding the implementation of the universal two-child policy; and 2017–2022 following the implementation of the universal two-child policy.
Abbreviation: BD=birth defect.

2016, potentially due to an increase in pregnancies among women of advanced maternal age. Our study indicates a spike in pregnancies among women over 35 in 2016, reaching 25.63% from an earlier 10%. This

TABLE 2. The prevalence of BDs in different maternal age groups from 2005 to 2020 (per 10,000 births).

Year	<20 years		20–25 years		25–30 years		30–35 years		35+ years	
	Proportion, %	PRE†	Proportion, %	PRE†	Proportion, %	PRE†	Proportion, %	PRE†	Proportion, %	PRE†
2005	0.08	277.78	22.58	108.62	52.78	84.11	19.65	112.96	4.91	172.12
2006	0.11	357.14	26.82	108.96	43.70	117.24	22.43	141.90	6.94	164.41
2007	0.12	269.61	22.69	97.20	43.08	105.01	25.35	92.10	8.76	131.51
2008	0.11	292.23	24.51	98.91	40.72	122.37	24.88	104.84	9.78	126.65
2009	0.24	249.24	27.94	97.06	36.28	108.62	24.92	103.41	10.62	110.11
2010	0.47	235.60	23.22	144.19	40.26	109.21	26.66	101.45	9.39	139.49
2011	0.41	337.42	29.66	162.71	36.59	186.96	24.05	164.98	9.31	215.24
2012	0.35	317.46	24.30	143.71	39.90	152.81	26.29	150.47	9.16	193.61
2013	0.57	273.35	22.08	133.31	41.29	164.14	26.54	145.46	9.52	151.82
2014	0.49	242.54	15.41	135.46	47.81	142.31	27.14	133.60	9.15	158.16
2015	0.69	263.65	13.31	179.91	43.91	189.51	27.67	172.08	14.42	205.03
2016	0.54	252.45	9.32	163.08	32.74	203.40	31.77	136.07	25.63	213.92
2017	0.62	290.70	10.71	233.98	31.48	254.97	29.22	309.57	27.97	314.31
2018	0.64	291.02	10.07	235.62	30.13	226.98	33.84	255.27	25.32	347.89
2019	1.32	293.17	10.92	237.75	31.12	230.58	32.07	249.54	24.57	328.41
2020	1.61	296.90	11.62	239.91	30.59	249.27	29.84	215.05	26.34	295.99
2021	1.63	301.63	12.02	241.63	29.36	251.36	31.63	225.36	25.36	312.36
2022	1.71	305.32	11.68	246.36	25.65	253.69	32.69	226.39	28.27	326.69
Total	0.65	272.91*	18.27	202.76	37.63	182.21	27.59	187.97	15.86	236.09*
AAGR	113.19	0.55	−2.68	7.05	−2.86	11.20	3.69	5.58	26.43	4.99

Abbreviation: BDs=birth defects; PRE=prevalence (per 10,000 births); CAT=Cochran-Armitage trend; AAGR=average annual growth rate.
* Chi-squared test $P<0.05$.
† CAT $P<0.05$.

TABLE 3. The prevalence of major birth defects from 2005 to 2020 (per 10,000 births).

Rank	Types of BDs	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total	AAGR
1	Congenital heart disease*	12.47	16.61	17.51	16.22	16.63	23.34	43.97	40.87	35.89	34.06	48.01	62.10	71.20	80.32	90.63	100.23	110.36	120.63	88.54	48.19
2	Polydactyly*	8.88	13.81	9.89	11.70	11.69	15.19	15.6	16.73	15.75	15.11	18.58	21.00	25.71	26.72	27.12	27.60	28.01	28.69	19.23	12.39
3	Cleft lip and/or palate	15.45	20.22	17.52	22.23	17.23	17.42	19.49	16.05	15.49	16.3	15.56	18.74	20.25	19.81	20.33	19.63	20.12	19.68	10.41	1.52
4	Hypospadias*	4.44	8.83	7.69	5.07	6.10	6.78	12.73	4.45	6.12	4.28	7.92	10.10	12.10	11.34	12.10	10.10	12.82	11.73	9.84	9.12
5	Syndactyly	3.38	3.20	3.41	2.68	2.55	3.33	3.32	3.59	3.49	3.57	5.63	6.90	7.89	6.96	6.70	4.80	5.10	5.20	5.35	2.99
6	Down's syndrome*	2.33	2.10	1.78	1.50	1.20	1.61	2.21	1.68	5.03	3.85	6.93	9.28	13.93	11.66	12.9	11.40	10.80	9.30	5.05	16.62
7	Other malformation of external ear*	1.90	2.40	1.95	3.34	1.35	0.74	2.70	2.47	3.36	3.20	3.53	2.89	6.82	6.56	5.40	3.90	3.70	3.90	4.36	5.85
8	Congenital hydrocephalus*	9.09	8.21	5.84	6.35	4.94	5.93	6.21	5.95	4.91	5.22	4.06	5.01	5.94	5.09	4.10	3.24	4.26	3.29	4.05	−3.54
9	Neural tube defects*	10.99	11.61	9.49	9.29	8.14	4.32	4.54	3.71	4.00	4.94	4.06	4.18	4.72	4.70	3.20	1.67	1.32	1.06	2.12	−5.02
10	Limb shortening*	4.23	5.60	2.92	4.68	2.55	2.47	4.18	3.26	3.61	2.93	4.32	3.19	4.80	4.20	3.90	2.15	2.05	1.98	3.61	−2.96

Abbreviation: BD=birth defect; AAGR=average annual growth rate; CAT=Cochran-Armitage trend.
* CAT $P<0.05$.

change likely stems from China's "universal two-child policy", allowing all women to have two children. Moreover, the traditional Chinese belief, deeming numerous sons as a source of abundant blessings, deeply entrenched in the society, also pose an effect. Consequently, following the policy's introduction, many women, particularly those of advanced maternal age, chose to have children. It is widely established

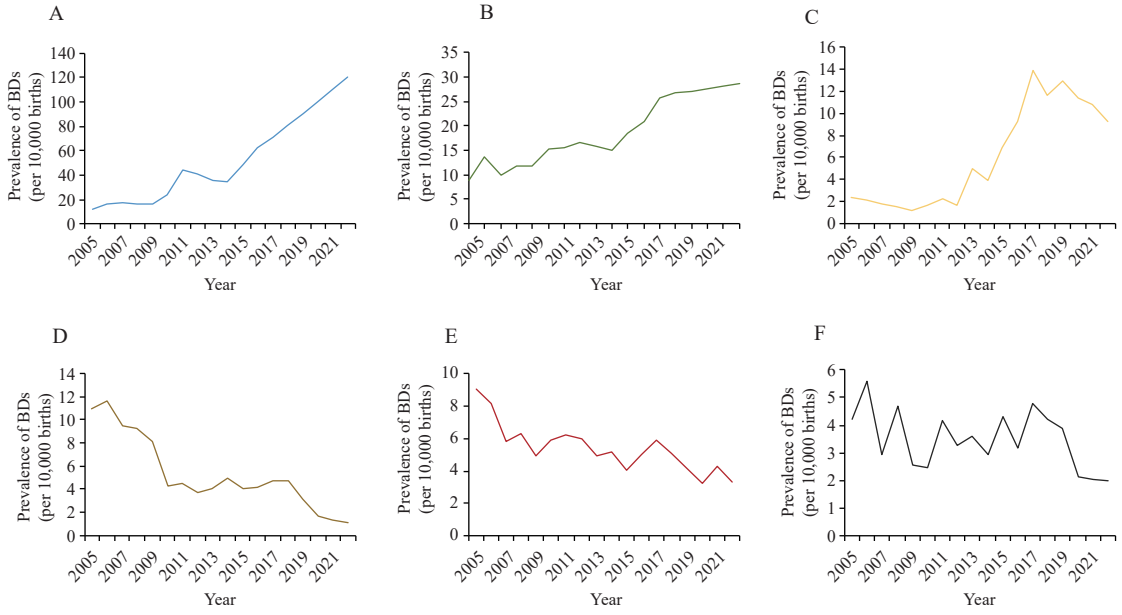

FIGURE 2. The prevalence of (A) congenital heart disease, (B) polydactyly, (C) Down's syndrome, (D) neural tube defects, (E) congenital hydrocephalus, and (F) limb shortening from 2005 to 2020.
Abbreviation: BD=birth defect.

through numerous studies that an increased maternal age poses risk factors for BDs (*10*), highlighting 2016 as a significant turning point in the rising birth defect trends.

Our findings revealed a higher prevalence of BDs in urban areas compared to rural areas, potentially due to increased work-related stress and environmental impacts in urban areas. Furthermore, birth defects grew faster in rural areas, a trend rarely seen in other studies. This observation could potentially be due to the inadequate awareness and application of preventive measures amongst pregnant women in rural areas, compounded by suboptimal lifestyle habits (*11*).

Our data shows a distinct "U" shaped pattern in the maternal age distribution of the prevalence of BDs, particularly among women under 20 and above 35. This trend mirrors earlier studies (*12*) and may be attributable to unhealthy lifestyles and reproductive challenges. We also highlight a rapidly growing proportion of pregnancies within these age groups, particularly among women under 20 — a demographic subgroup that has previously garnered little research attention. In China, pregnancies in women under 20 are commonly unintended and frequently result in induced abortion, which poses substantial health risks.

Our time trend analysis examined the prevalence of key BDs, revealing a notable increase in the prevalence of congenital heart disease (CHD), aligning with the findings of numerous studies (*13*). It is well understood that CHD originates from complex, multifactorial causes. The noted escalation in prevalence can be attributed to advancements in diagnostic and screening techniques, lifestyle behaviors of parents, genetic and environmental contributors to BDs, or a combination thereof. The widespread implementation of ultrasound technology in obstetrics should not be dismissed. A significant growth inflection point was observed for CHDs in our study in 2011. This corresponds with the introduction of free neonatal screenings for CHD in Jinan that year. The percentage of neonatal screenings soared from an average of 35.67% before 2011 to 85.36% thereafter, leading to the detection of previously undiagnosed cases, such as mild VSD or ASD. Similar observations have been reported in other scholarly articles (*14*).

Our research also indicates a notable decrease in the prevalence of neural tube defects, which can be attributed to the widespread promotion of folic acid programs in Jinan. The protective effect of folic acid is well-supported by multiple studies (*15*). Following the introduction of free folic acid for expectant mothers into public health initiatives in 2009, nearly 95% of them began a regular intake of folic acid during their pregnancies. This is likely associated with the marked decrease in the prevalence of neural tube defects in Jinan post-2010.

Our study has certain limitations. First, the birth defect data was hospital-based. Although the

monitoring phase extended up to 12 gestation weeks, any birth defects occurring prior to this period or outside of hospital settings may have been overlooked. Second, environmental hazards and unhealthy lifestyles play a significant role in the incidence of birth defects. However, due to data limitations, we couldn't fully assess the impact of these factors on Jinan's birth defect rates, indicating the need for additional research. Third, the annual variation in the monitoring time duration for birth defects could potentially adversely affect the trend analysis for birth defects. Lastly, given the extended monitoring period, changes in diagnostic criteria or improvements in diagnostic methods were inevitable, meaning that the prevalence of birth defects could be underestimated.

In summary, there has been a notable escalation in the prevalence of BDs in Jinan, with the growth rate in rural areas surpassing that in urban regions. Data indicates that mothers over 35 and under 20 exhibit a pronounced BD prevalence relative to other maternal age groups, and representation within these age groups is also dramatically rising. Furthermore, there is a marked increase in the prevalence of congenital heart disease, while the prevalence of neural tube defects shows a decrease. Targeted interventions for expectant mothers in rural territories, as well as those in the aforementioned age groups, are imperative.

Acknowledgements: Appreciation is expressed to all the participants for their contribution.

doi: 10.46234/ccdcw2023.184

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Submitted: August 24, 2023; Accepted: September 11, 2023

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Review

A Review of Pathogens Transmitted by the Container-Inhabiting Mosquitoes, Aedes Albopictus, A Global Public Health Threat

Wenrong Zhang[1,&]; Jinna Wang[2,&]; Qinmei Liu[2]; Zhenyu Gong[2,#]

ABSTRACT

Dengue virus (DENV), Chikungunya virus (CHIKV), and Zika virus (ZIKV) are highly pathogenic human arboviruses transmitted by the *Aedes (Stegomyia) albopictus (Skuse) (Diptera: Culicidae)* or *Ae. Albopictus* mosquito. These arboviruses are responsible for causing fever, hemorrhagic conditions, and neurological diseases in humans post-bite from an infected *Aedes* mosquito. Over the past 80 years, the *Ae. albopictus* has infested every habitable continent, bar Antarctica, thereby escalating the probability of global insect-borne infectious disease outbreaks. This research follows the global transmission pattern of *Ae. albopictus* and provides a summary of disease prevention and control strategies for mosquito-borne infections, as implemented by the World Health Organization (WHO) and both Asian and European countries. Consequently, this study can aid in the prevention and control of mosquito-borne diseases while acting as a basis for international collaboration on effectively managing arbovirus infection issues in public health.

INTRODUCTION

Globally, 537 arboviruses have been identified, with over 150 presenting a significant risk for transmission to humans or animals (*1*). *Ae. albopictus* serves as a vector for several highly pathogenic viruses to humans, including Dengue, Chikungunya, Zika virus, among others. Over the last three to four decades, the presence of *Ae. albopictus* has been reported in more than 70 countries, extending its global distribution to all continents except Antarctica (*2*). A recent study developed a model predicting the presence of *Ae. albopictus* in 197 countries by the year 2080 (*3*).

Global socioeconomic development, rapid urbanization, increased human and goods mobility, and climate change have all contributed to an escalating risk of vector-borne diseases. Moreover, with the resurgence of regional and international population movement and trade transactions as the world begins to navigate the post era of Coronavirus 2019 (COVID-19) pandemic, the global spread of vector-borne viruses has similarly increased. This study seeks to provide an overview of pathogenic virus species and infection rates carried by *Ae. albopictus* worldwide, summarizing strategies undertaken by global organizations for mosquito-borne disease prevention and control across various regions in furtherance of One Health objectives.

AEDES ALBOPICTUS

The *Aedes (Stegomyia) albopictus (Skuse) (Diptera: Culicidae),* more commonly known as the Asian tiger mosquito, originates from Southeast Asia but is broadly dispersed within tropical and subtropical regions, particularly thriving and reproducing in densely populated urban environments. It exhibits peak activity during daylight hours (*4*). Its vectoring competency is lower than that of *Aedes aegypti (Ae. aegypti)*, notwithstanding, its higher tolerance to colder climates allows for a wider range of dispersion (*5*). Upon biting and feeding on animal or human hosts, *Ae. albopictus* transmits pathogenic viruses, thereby causing symptoms of disease.

PATHOGENIC PATHOGENS

Current research indicates that *Ae. albopictus* mosquitoes can transmit numerous pathogens including Dengue virus (DENV), Zika virus (ZIKV), Chikungunya virus (CHIKV), Japanese encephalitis virus (JEV), West Nile virus (WNV), Mayaro virus (MAYV), and Tahyna virus (TAHV), among others, prompting outbreaks and epidemics of vector-borne diseases in assorted regions (*4*). In the ensuing section, we will provide a detailed analysis of the pathogenic viruses that *Ae. albopictus* can harbor.

Dengue virus: The DENV belongs to the *Flavivirus*

genus within the family Flaviviridae, encompassing four primary serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. These serotypes are globally prevalent. However, the Mustafa study discovered a potential fifth serotype (*1*). Dengue fever (DF) manifestations differ across serotypes, typically initiating with a rapid onset of high fever, headache, back, bone, joint, and muscle pain, petechiae on the skin, swollen lymph nodes, and a reduction of white blood cells and platelets. DENV was initially isolated in Japan in 1943 from the serum of an infected patient using suckling mice (*6*). The first recorded outbreaks of DF occurred in Jakarta, Indonesia, and Cairo, Egypt, in 1779 (*7*). Currently, DF is acknowledged as the most widespread and rapidly proliferating mosquito-borne viral disease affecting humans, with high prevalence in Africa, Asia, Australia, and the Americas (*8*). *Ae. aegypti* and *Ae. albopictus* are key vectors in DENV transmission (*5*). Interestingly, the virus was first isolated from *Ae. albopictus* females captured during an outbreak in Libreville, Gabon, while all *Ae. aegypti* specimens tested negative (*9*). Genotype 1 DENV was detected in *Ae. albopictus* mosquitoes sampled during a localized DF outbreak in Wenzhou City, Zhejiang Province, China, in 2018 (*10*). Moreover, positive DENV isolation rates from *Ae. aegypti* and *Ae. albopictus* in China were found to be 13% and 1%, respectively (*10*). Another study reported an 8.33% DENV-positive rate in *Ae. albopictus* overwintering eggs collected from the West Lake area in Hangzhou (*11*).

Zika virus: The ZIKV is a *Flavivirus* arbovirus characterized by two distinct subtypes: African and Asian. ZIKV infection symptoms can include low-grade fever, maculopapular rash, headaches, arthralgia, myalgia, weakness, and nonsuppurative conjunctivitis. The virus was first identified in 1947 from a rhesus monkey inhabiting the "Zika jungle" in Kampala, Uganda and later found in Ae. aegypti mosquitoes within this same forest (*12*). The inaugural human case of ZIKV was reported in Nigeria in 1954 (*13*).

Starting from May 2015, the virus has sparked large-scale outbreaks across the Americas, most notably, in Brazil. Of considerable concern is the association of ZIKV infections in pregnant women with fetal microcephaly. This link has catapulted the Zika disease into a global health concern and contributed to ZIKV's spread to 59 countries across the globe (*14*).

While *Ae. aegypti* has been identified as the primary mosquito vector transmitting ZIKV, the virus has also been confirmed in *Ae. albopictus* and *Aedes. africanus* mosquitoes (*15*). Research by Jeronimo Alencar and colleagues has unveiled ZIKV infections and natural vertical transmission within Brazil's *Ae. albopictus* (*16*). In 2020, a study in China investigated the oral susceptibility and vector competence of ZIKV within *Ae. albopictus* Guangzhou beads. It was discovered that, six days after infection, a prevalence of 36.4% of the virus was found in the saliva of *Ae. albopictus* mosquitoes (*17*).

Chikungunya virus: CHIKV falls under the *Togaviridae* family, specifically the genus *Alphavirus*. It boasts four genotypes: West African (WA), East/Central/Southern African (ECSA), Asian, and Indian Ocean type (IOL) (*18*). Typical manifestations of the virus's acute phase are sharp instances of fever, arthralgia affecting the knees and shoulders, and extreme pain due to arthritis. Initially identified in 1953, CHIKV originates from Africa, with the first isolation recorded in Tanzania. The inaugural *Ae. albopictus*-vectored strain of CHIKV, appearing as an IOL strain, was discovered on Reunion Island in the Indian Ocean (*19*). In Italy, CHIKV's genome has been identified within the *Ae. albopictus* mosquito, pointed as the vector instigating local Chikungunya fever outbreaks (*4*). Current epidemiological studies have not produced evidence suggesting that *Ae. albopictus* can transmit the Asian genotype of CHIKV (*18*). The mosquito-borne illness, once restricted to South Africa, Southeast Asia, and selective tropical regions in India, has now breached other subtropical nations (*18*). Evolution of CHIKV enhances its compatibility with *Ae. aegypti* or *Ae. albopictus*, thereby improving the virus's transmission within populations. CHIKV's main adaptation for increased infectivity is promoting the reproductive capabilities of *Ae. Albopictus* (*18*).

Japanese encephalitis virus (JEV): JEV is a zoonotic disease transmitted by mosquitoes. While infection is often asymptomatic, severe cases can lead to acute encephalitis and neurological sequelae (*20*). Classified under the *Flavivirus* genus of the *Flaviviridae* family, JEV is a single-stranded positive-stranded RNA virus. Five genotypes of JEV exist, with genotype 1 strains increasingly prominent in China (*21*). Currently, JEV is endemic in 24 countries across South and Southeast Asia, Japan, northern Australia, and Oceania (*22*). Seventeen species of mosquitoes are known to transmit JEV, while an additional ten species are potential carriers (*20*). *Aedes* darkis, *Aedes* mansoni, *Aedes* spp., and *Culex trituberculatus* (*Cx. trituberculatus*) serve as vectors for JEV, with *Cx. trituberculatus* acknowledged as the primary vector in China and most other Asian

countries (*22*). JEV was first discovered in Taiwan, China, in 1895, with its isolation from *Ae. albopictus* yielding a minimum infection ratio (MIR) of 0.56% (*23*). Subsequent research has demonstrated that JEV can survive for two months in desiccated *Ae. albopictus* eggs (*24*).

West nile virus(WNV): a member of the *Flaviviridae* family, is a zoonotic arbovirus transmitted between mosquitoes and birds. Humans and other animals primarily act as terminal hosts. WNV has been responsible for diseases in humans across all continents except Antarctica (*25*). Most individuals infected with WNV remain asymptomatic, while a minute fraction manifests symptoms such as WNV encephalitis, meningoencephalitis, and meningitis (*26*). The virus has been reported in Africa, Asia, Europe, Australia, and North America, identifying it as the most widely spread mosquito-borne *flavivirus* globally (*27*). The risk of acquiring a vector-borne disease through a mosquito bite remains substantial, and the virus has been detected in a variety of mosquito species, including *Aedes* (*28*), *Anopheles* (*29*), and *Culex mosquitoes* (*30*). WNV was first isolated in Chinese mainland in 2011 from mosquitoes in Jiashi County, Kashgar Region, Xinjiang, following outbreaks of viral meningitis and encephalitis caused by WNV (*31*). In laboratory experiments, Chinese researchers fed *Cx. trituberculatus, Cx. quinquefasciatus, Cx. pipiens*, and *Cx. bitaeniorhynchus* mosquitoes blood infected with WNV. They found that all four mosquito species could transmit the virus, with *Cx. trituberculatus* showing the highest infection and transmission rates (87.5% and 74.2%), respectively (*30*). Some studies have identified local WNV transmission in China through serological assays (*27*). Moreover, experimental studies have demonstrated that WNV can survive in *Ae. albopictus* eggs and continue to be transmitted to mosquito larvae once the latency is disrupted (*28*).

Mayaro virus: The Mayaro virus (MAYV; family *Togaviridae*, genus *Alphavirus*) is a single-stranded positive-stranded RNA virus, which produces symptoms akin to DENV infection, with acute joint pain being the most prominent clinical symptom of MAYV infection (*32*). The virus was first isolated in 1954 from ailing forestry workers in Trinidad, while subsequent instances of human infection and minor outbreaks have been documented in northern regions of South America (*33–34*). Although the majority of recorded cases have been associated with humid, flood-prone forested areas, there has been an increasing, worrisome trend towards urbanized cases of MAYV transmission (*35–36*). Presently, the virus is primarily endemic in South America, with Brazil being the most affected (*37*). Various mosquito species, including *Ae. aegypti*, *Culex*, and *Ae. darkis* are vectors of MAYV transmission (*33*). Research conducted on the Brazilian strain of *Ae. albopictus* indicates that this species can act as a vector for MAYV transmission, contingent upon a sufficiently high population and extensive incubation period to allow virus proliferation (*38*).

Tahyna virus(TAHV): TAHV originated from the *Bunyaviridae* family, specifically, the genus *Orthobunya* virus within the California serogroup. Infections typically manifest in the form of fever and flu-like symptoms. However, it can also lead to more severe conditions such as pneumonia and pleurisy, acute arthritis, pharyngitis, and in rare instances, central nervous system dysfunction. TAHV holds the distinction of being the first arbovirus isolated in Europe, specifically from *Aedes*. *Caspius* and *Aedes*. *Vexans* collected in the Tahyna and Krizany villages in Eastern Slovakia (*39*). The virus subsequently spread throughout Europe, with Calzolari et al. (2021) discovering a 4% positivity rate in *Ae. albopictus* during mosquito surveillance in Emilia-Romagna (*40*). TAHV was first isolated in China from *Culex* mosquitoes in Xinjiang in 2006, with subsequent potential human transmission inferred from seropositive tests among febrile patients (*41*). Since then, the virus has also been identified in other mosquito species in Qinghai and Inner Mongolia (*42*).

CARRIAGE STATUSES OF COMPOUND VIRUSES

Ae. albopictus mosquitoes function as carriers of DENV, CHIKV, and MAYV, among other viruses. As a result, regions inhabited by this mosquito species often experience a high incidence of viral co-vectors and multiple instances of mosquito-borne illnesses within their populaces. In an increasing volume of investigations, this particular vector has been found residing simultaneously alongside multiple viruses. Wazeye 2010 first identified the potential for a single *Ae. albopictus* mosquito to contract both CHIKV and DENV during a controlled infection experiment (*43*). The first reported case of Dengue-Chikungunya co-infection took place in Thailand in 1962 as documented by Nimmannitya et al. (*44*). Instances of worldwide Dengue-Chikungunya co-infections have been found and continue to exist in such regions as

Africa, Southeast Asia, the Eastern Mediterranean, and the Western Pacific (*43*). There are even reports of three patients having Dengue, Chikungunya, and Zika co-infections presenting with fever syndrome along the Colombia-Venezuela border (*45*). Genetic testing conducted on an 8-year-old boy from Haiti in 2015, residing in a non-forested region and exhibiting fever symptoms, demonstrated infections of both DENV-1 and MAYV (*46*).

Prevention and Control Policies for Vector-Borne Diseases

The global community is showing growing concern over mosquito-borne diseases. Consequently, the proactive prevention and control of arthropod diseases has become a widely discussed topic of paramount importance.

The global propensity for zoonotic diseases to cross borders necessitated a comprehensive approach, which led the American Veterinary Medical Association (AVMA) to introduce the "One Health" concept in 2007. This term encapsulates the intricate interplay between humans, animals, and the environment in the propagation of diseases. Critical issues addressed by One Health encompass zoonotic afflictions, antimicrobial resistance, food safety and security, vector-borne diseases, environmental contamination, and various other health challenges common to humans, animals, and the environment. The promotion of the One Health ethos is fostering opportunities for establishing frequent interrelationships between public health disciplines and ancillary fields, thus facilitating interdisciplinary cooperation in education and scientific research.

In October 2015, the Fifth Plenary Session of the 18th Central Committee of China's Communist Party (CPC) officially stated the upcoming 15-year span as a crucial strategic opportunity for enhancing the establishment of a healthier China. This undertaking represents a significant initiative to proactively contribute towards global health governance and meet the international obligations of the 2030 Agenda for Sustainable Development.

In October 2016, China's Communist Party Central Committee and the State Council issued the blueprint for the "Healthy China 2030" initiative. This program showcases an expansive plan of action focused on advancing the protection of citizen health. It articulates the infrastructural provisions necessary for safeguarding the public's health. The outline details China's pledge to conduct wholesome patriotic health movements, implement a thorough control and prevention strategy against disease-bearing organisms primarily through environmental management, and to manage the health concerns in both urban and rural environments synergistically.

Moreover, by 2030, China aspires to establish numerous exemplar cities, towns, and villages to support the notion of healthy living. Plans also include setting up state-of-the-art monitoring and early warning systems for global infectious disease information, enhancing the international travel health information network, offering real-time and efficient health guidelines for global travel, and constructing a world-class international travel health service system to safeguard the wellbeing and safety of international arrivals and departures.

Finally, China intends to enhance the surveillance and control mechanisms aimed at disease carriers and various major infectious diseases at international border crossings. Proactive efforts will be directed toward preventing, controlling, and responding to public health emergencies originating outside the country.

In light of the global duality of threat and burden posed by both new and re-emerging vector-borne diseases and imported and endemic vector-borne diseases, the 70th World Health Assembly initiated the "Global Vector Control Response 2017–2030" in 2017. This action plan indicates that 80% of the global population is at risk from one or more vector-borne diseases, 17% of the global burden of infectious diseases is attributable to vector-borne infections, and each year, vector-borne diseases cause more than 700,000 fatalities (*47*). Countries across the globe have begun to implement innovative prevention and control strategies, heralding a new era for the international prevention and control of vector-borne diseases.

As outlined in the 2020 WHO Vision for the Future of Work with Western Pacific Member States and Partners Towards the Healthiest, Safest Regional Future, the gravest collective concern for the Western Pacific region revolves around the health impacts of climate and environmental changes. The WHO remains steadfast in its commitment to addressing the "unfinished business" of controlling and eliminating infectious diseases as public health threats (*48*).

In 2022, China put forth plans to finalize its public health infrastructure, bolster its main epidemic prevention and treatment protocol, and enhance its emergency response capabilities. This move aimed to

effectively manage the propagation of critical infectious diseases. Concurrently, a national administration for disease prevention and control was established, assuming full responsibility for mitigating disease and especially curtailing the sudden outbreak of infectious diseases. Alongside these structural revisions, the government vowed to foster outstanding talent capable of addressing substantive public health challenges. Additionally, there is an emphasis on significantly augmenting the caliber of scientific research in disease prevention and control sectors, with a particular focus on nurturing expertise in tracing infectious disease origins.

TECHNIQUES AND STRATEGIES FOR VECTOR CONTROL

At present, most virus-specific drugs and vaccines for mosquito-borne diseases are in the developmental stages, with their safety and efficacy yet to be definitively established. Consequently, preventative measures and control strategies for these diseases emphasize the primordial tenets of "controlling the source of infection, obstructing the transmission route, and protecting the vulnerable population". The Centers for Disease Control and Prevention (CDC) advocates for mosquito vector management and bite avoidance as the primary preventative measures for mosquito-borne diseases such as Dengue, Zika, and Chikungunya. Essential to these efforts are robust systems for monitoring mosquito vectors, rapidly detecting and curbing potential epidemics (*49*).

Some researchers propose that, in countries where *Ae. albopictus* has not yet established a foothold, the primary focus should be on refining the detection of this species at entry points and beyond, leveraging advancements in vector biomonitoring and genomic technologies (*3*). A comprehensive practical study on effective mosquito vector control methods in Latin America and the Caribbean suggests that an integrated approach that emphasizes community engagement appears most effective in reducing the transmission of diseases through *Ae*. mosquitoes (*50*).

China's commitment to public health is reflected in their explorations of the "One Health" concept and innovative initiatives such as the "Mosquito-Free Village" pilot project launched in Zhejiang Province in 2016. The project, a grassroots effort targeted at long-term vector control, set the stage for the province's development in 2021 of the first phase of the "mosquito and fly eradication villages." This initiative provides both a theoretical and practical foundation for environmentally sustainable, long-lasting programs focused on biological vector management and the prevention and control of mosquito-borne disease outbreaks, such as dengue fever (*51*).

These programs emphasize the use of environmental, physical, and chemical control measures to decrease the population and reproductive capacity of mosquito vectors, thereby reducing the risk of mosquito-borne virus transmission to humans. Concurrently, each district implements active mosquito monitoring programs tailored to the locale's geographical and climatic attributes. Additionally, local communities are encouraged to participate in integrated disease vector organism management efforts (*52*).

CONCLUSION

The mosquito-borne virus carried by *Ae. albopictus* is now highly prevalent and globally transmitted, significantly affecting not only human health but also the worldwide economic landscape. A comprehensive examination of these mosquito-borne viruses, with a focus on the molecular analysis of their genomes, will help in the development of vaccines and effective therapeutic options. Consistent monitoring of mosquito populations that serve as carriers, combined with risk assessment and forecasting through mathematical models, aids in the early identification of potential disease outbreaks and epidemics. Every nation bears a responsibility to aid in thwarting the dissemination of arboviruses. Further, the practice of sharing consolidated and successful prevention and control strategies will bolster efforts to achieve the One Health objective.

Conflicts of interest: No conflicts of interest.

doi: 10.46234/ccdcw2023.185

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Submitted: August 11, 2023; Accepted: October 31, 2023

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Review

A Scoping Review of Tools and Techniques on Evaluating Population Health and Healthy Life Expectancy

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ABSTRACT

The concept of healthy life expectancy (HLE) integrates the ideas of life expectancy and health status, providing a valuable metric to evaluate both the length and quality of life. This paper seeks to aid policymakers in creating an inclusive HLE indicator system through a systematic review of methodologies for defining and measuring HLE, along with relevant published studies' descriptions. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews statement, two English language literature databases were researched from January 2020 to April 2023. Findings from empirical HLE-related studies were analyzed by extracting data on the study area, design, population, healthy state measurement tools, and results of studies using HLE indicators. The current analysis encompassed 48 empirical studies. Researchers discerned 11 unique HLE indicators within this corpus, each concentrating on a particular aspect. Furthermore, the analysis revealed 18 diverse instruments for evaluating health statuses, each varying in its definition of a healthy state, dimensions of measurement, and the categories of data employed. Therefore, merging global health concepts, HLE indicators, methodologies for assessing healthy states, and applied research demonstrations is essential for a consolidated HLE indicator system creation. tes, and applied research demonstrations are essential for a consolidated HLE indicator system creation.

Healthy life expectancy (HLE) is an instrumental gauge that accounts for mortalities and morbidity conditions resulting from diseases or disabilities. This measure estimates the average number of years an individual can anticipate living in optimal health. Consequently, HLE serves as a fundamental tool in developing health objectives and customizing health strategies, as evidenced in national health schemes.

The World Health Organization (WHO) defines health as a condition of complete physical, mental, and social well-being rather than merely being devoid of disease or affliction (*1*). This inclusive definition acknowledges the multifaceted nature of health. Researchers have crafted various indicators related to health-related quality of life (HRQoL) (*2*). These indicators concentrate on diverse facets, such as physical function, disease impact, and self-perception (*3*). Nonetheless, the current set of indicators lacks the capacity to evaluate population health across these diverse dimensions comprehensively. Nations worldwide are increasingly adopting their bespoke systems to evaluate HLE, highlighting a critical absence of a globally recognized concept, methodology, or theoretical framework for HLE. In this context, recent HLE research within China has primarily focused on regional dimensions, revealing a significant shortfall — the lack of a universally endorsed approach for empirical analysis. This gap necessitates an urgent integration of international HLE learnings, tailored specifically to China's unique socio-cultural landscape, a need further catalyzed by the vigorous advancement of the "Healthy China" and "Healthy Aging" campaigns. Consequently, this project is principally dedicated to mitigating this empirical deficit by developing comprehensive tools for health assessment and establishing a coherent HLE indicator framework, distinctly aligned with China's national prerequisites.

METHODOLOGIC FRAMEWORK

A scoping review encapsulates the synthesis of evidence intending to identify and chart relevant pointers on a specific theme, framework, idea, or issue, adhering to pre-set inclusion criteria. Unlike traditional systematic reviews, its core objective is to provide an extensive overview of the accessible evidence without

emphasizing quantitative or qualitative data synthesis. Consequently, the guiding research questions in a scoping review are generally broader in scope (*4*). The most updated advice on executing scoping reviews is incorporated in the guidelines put forth by Joanna Briggs Institute (JBI) in 2020 (*5*), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (*6*). Both the JBI guidelines and the PRISMA-ScR offer contemporary and comprehensive guidance for authors embarking on scoping reviews. They further provide a structured layout for reporting the scoping review process. Due to the unique features of the JBI and PRISMA-ScR frameworks when juxtaposed against other review methodological frameworks, we have chosen them to conduct our scoping review to guarantee more suitable and insightful outcomes.

Research Objectives and Questions

This study adheres to the population, concept, and context (PCC) paradigm, as suggested by the JBI, for establishing research questions and objectives (*5*). The dual purpose of this scoping review is to: 1) examine measurement devices for evaluating the health status of populations and metrics for determining HLE; 2) characterize the properties and structure of current tools and indicators. The research objectives steering this review include: 1) Identifying indicators that are utilized for evaluating population health statuses; 2) Determining measurement tools that are associated with these identified indicators; 3) Documenting the characteristics of these tools and indicators.

Search Strategy

A comprehensive search was conducted across two literature databases, namely, PubMed and Web of Science, encompassing articles published from January 2020 to March 2023. The search strategy followed the guidelines provided by JBI and PRISMA-ScR, adhering to the specific search criteria and syntax for PubMed and Web of Science. A blend of subject headings and words was utilized, primarily focusing on terms correlated with healthy life expectancy, the state of health, and respective measurement instruments. The search encompassed the following MeSH terms: "Healthy Life Expectancy" [Mesh] OR "Healthy State Life Expectancy" [title or abstract] OR "Health Adjusted Life Year" [Mesh]".

Evidence Selection and Appraisal

The initial analysis entailed implementing a duplication elimination process via Endnote X9. The subsequent step consisted of conducting a manual review of the remaining articles. This evaluation involved an inspection of the abstracts and the titles, followed by a full-text feasibility assessment. This study was steered by multiple health interpretations, including physical, mental, and social well-being. Special emphasis was placed on the assessment of healthy states across these parameters and pinpointing the corresponding indicators for HLE.

During the review stage of titles and abstracts, the criteria for article inclusion hinged upon incorporating the keyword "HLE" in either the title or abstract, regardless of whether the paper's primary focus was HLE. Consequently, articles that did not pertain to HLE or were not peer-reviewed were omitted from the study.

In the prior phase, unresolved consensus regarding an article automatically progressed to the full-text feasibility assessment. In the event of any disagreement during this phase, the team carefully reassessed the inclusion/exclusion criteria to achieve consensus. Our study selection criteria required at least one appraisal of health state dimensions and an evaluation of the corresponding HLE. Studies that merely mentioned HLE without conducting a health state assessment or HLE measurement, or those unavailable in full text, or not in written English, were excluded (Figure 1).

Data Extraction and Synthesis

The process of graphing data is a valuable analytical tool enabling comprehensive literature analysis, identifying key concepts, and establishing underlying themes. In our study, we utilized a standardized Microsoft Excel sheet for data collection. One researcher initially retrieved the information, while another independently verified the data for accuracy. We then summarized the extracted data based on various study features such as national origin, publication date, and authorship. Moreover, we detailed the study design and sample information, including methodology, sample size, and the specific demographics and geographic regions targeted. Additionally, we gathered data on the tools employed to evaluate health status and healthy life expectancy indicators. Our findings are reported descriptively, and we have synthesized associations and made comparisons of indicators where relevant.

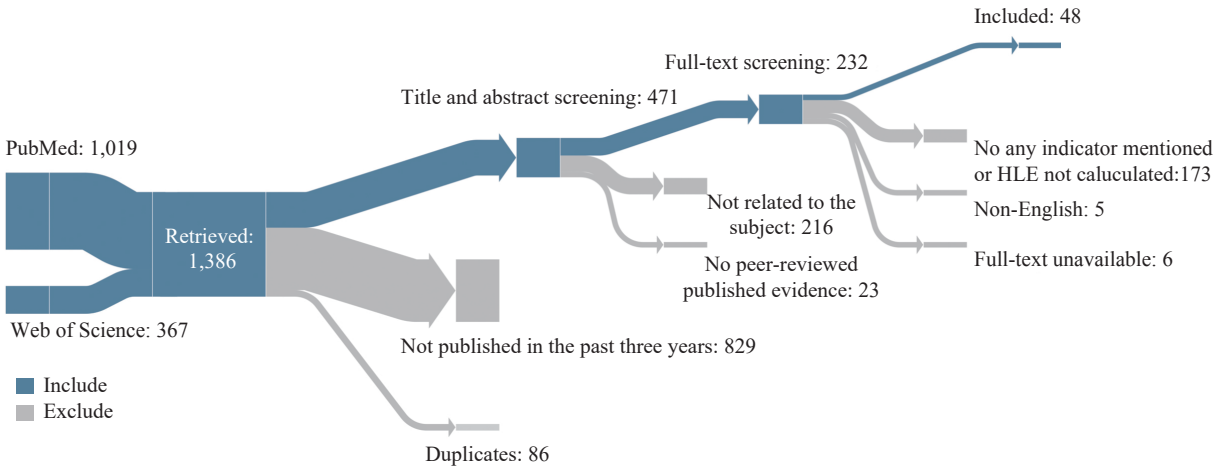

FIGURE 1. Flow chart for the selection process.
Abbreviation: HLE=healthy life expectancy.

RESULT

Literature Screening

In an evaluation of 1,386 articles assembled from database searches, with 1,019 sourced from PubMed and 367 from the Web of Science, only 48 studies met the defined inclusion criteria and were subsequently included in the final synthesis (Figure 1).

Summary of Empirical Studies on HLE

This research encompassed 48 studies from 22 countries, utilzing 19 distinct measurement tools to assess the general health status of populations in 37 nations or regions and calculate 11 relevant HLE indicators. The employed methodologies were predominantly cross-sectional (n=26) or longitudinal (n=22). A significant focus was on participants aged 60 and over, as depicted in Figure 2.

Indicators Classification and Measurement Tools

Indicators classification: The classification of indicators is shown in Table 1. The HLE indicators were classified into healthy state life expectancy (HSE) indicators and healthy adjusted life expectancy (HALE) indicators according to the Réseau Espérance de Vie en Santé (REVES) classification. Out of the 48 studies included in our analysis, 9 HSE indicators were measured. This study further classified these HSE indicators into disability-ree life expectancy (DFLE), disease-free life expectancy (DisFLE), self-rated healthy life expectancy (SRH), and other customized HSE indicators.

In the surveyed literature involved in this study, DFLE emerged as the most frequently assessed HSE, with a total of 62 occurrences across various studies. Furthermore, DisFLE was evaluated through five indicators, constituting seven measurements. SRH, also known as healthy life expectancy, comprised another considerable focus of this research, observed in four countries or regions.

HLE represents a category within the REVES network, specifically highlighted by HALE. Two key indicators within HALE are utilized: disability-adjusted life expectancy (DALE) and quality-adjusted life expectancy (QALE). These indicators have been incorporated in the studies under review, with DALE twice and QALE included once.

Measurement tools: Figure 2 indicates eight different tools that were utilized to assess disability status. The Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL) and Groningen Activity Restriction Scale (GARS) were recorded as the predominant tools, with usage frequencies of 26 and 18 times, respectively.

To gauge the manifestation of disease, we utilized the mini-mental state examination, Patient Health Questionnaire-2, and the Generalized Anxiety Disorder-2 as evaluative metrics to determine the health status in Cognitive-Impairment-Free Life Expectancy (CIMFLE), Depression-Free Life Expectancy (DeprFLE), and Anxiety-Free Life Expectancy (AFLE) respectively. Furthermore, we employed self-reported measures to appraise the presence of chronic disease, depression, and anxiety in the Chronic Disease-Free Life Expectancy (CDFLE) and Depression and Anxiety-Free Life Expectancy

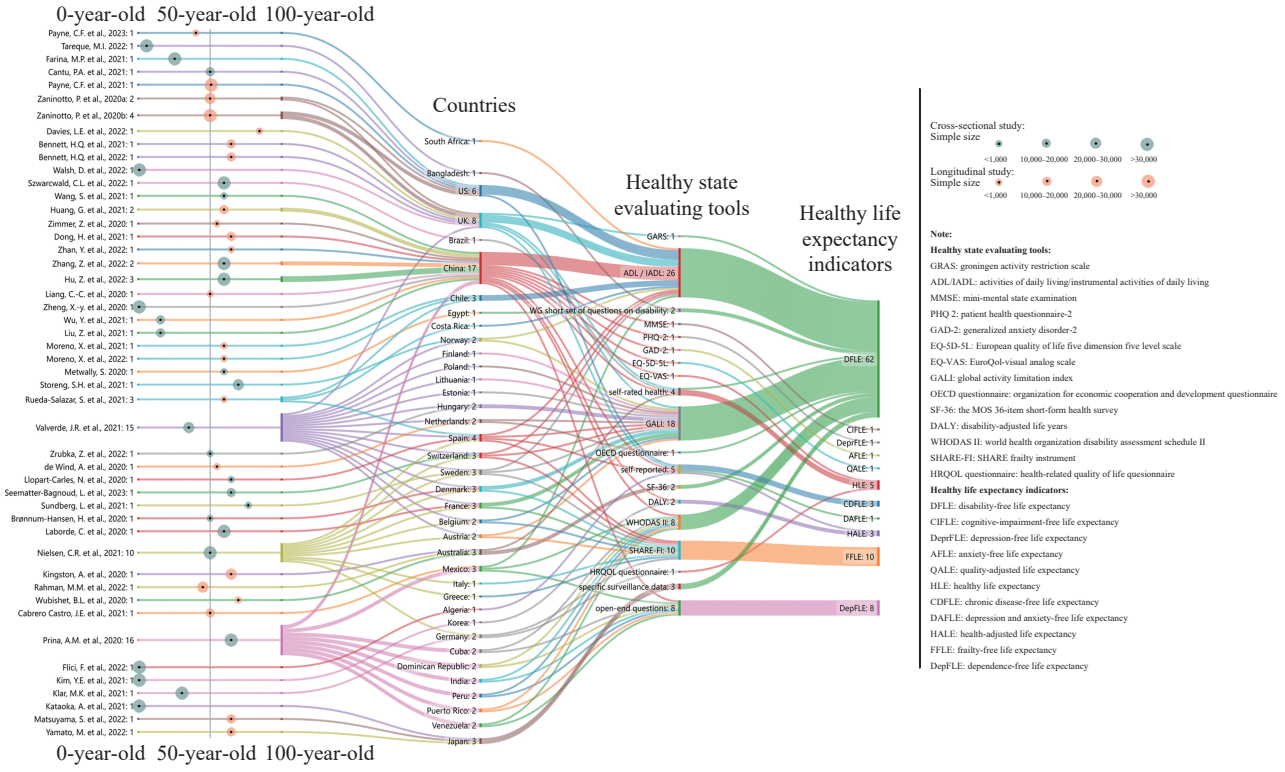

FIGURE 2. Characteristics of included researches.

TABLE 1. Summary of HLE indicators of included studies from recent three years, globally, classified by REVES.

Category	Dimension	Indicator	Count	Percentage (%)
Healthy state expectancy			91	96.81
	Disability	Disability-free life expectancy	62	65.96
		Cognitive-impairment-free life expectancy	1	1.06
		Depression-free life expectancy	1	1.06
	Disease	Anxiety-free life expectancy	1	1.06
		Chronic disease-free life expectancy	3	3.19
		Depression and anxiety-free life expectancy	1	1.06
	Perceived health	Self-rated healthy life expectancy	4	4.26
	Others	Frailty-free life expectancy	10	10.64
		Dependence-free life expectancy	8	8.51
Health adjusted life expectancy			3	3.19
	Disability-adjusted	Disability-adjusted life expectancy	2	2.13
	Quality-adjusted	Quality-adjusted life expectancy	1	1.06

Abbreviation: REVES=Réseau Espérance de Vie en Santé.

(DAFLE) cohorts..

Four studies included in this analysis utilized self-assessed measures to evaluate the comprehensive health status of the subject pool, covering diverse facets of individual physical, psychological, and social adaptation.

Two studies independently gauged health status using distinct methodologies. The initial study employed the Survey of Health, Ageing and Retirement in Europe-Frailty Instrument (SHARE-FI) questionnaire for its assessment, while the subsequent study leveraged open-ended questions. Upon completion, researchers derived two indicators of health state evaluations, namely; Frailty-Free Life

Expectancy (FFLE) and Dependence-Free Life Expectancy (DepFLE).

In regard to HALE, two studies leveraged disability-adjusted life years (DALY) as a measure, whereas another study deployed the European Quality of Life Five-dimension Five-level Questionnaire (EQ-5D-5L) instrument to evaluate the subjects' quality of life.

DISCUSSION

HLE has become a key component of current population health research and frameworks, with a broad spectrum of countries and regions adopting it as a crucial metric for assessing their populations' overall health status. Nonetheless, calculating and comparing HLE often poses challenges due to variations in health dimensions and the absence of consensus on validated assessment tools.

Healthy State Expectancy

HSE quantifies the anticipated duration of an individual's life in a healthy condition. The designated endpoint for HSE calculations can differ between studies, potentially encompassing aspects such as disability, distinct diseases, or self-perceived health.

Indicators of HSE bear limitations in their capacity to fully represent the health spectrum of a population. These markers typically concentrate on one aspect, such as disability, to the exclusion of equally crucial factors like disease prevalence. For instance, employing the DFLE parameter discounts the presence of diseases or conditions. In contrast, the DisFLE combines disease prevalence and mortality data to delineate a healthy state but overlooks certain unrecognized factors contributing to poor health. Fluctuations in the calculated DFLE values can stem from disparities in the assessment tools implemented to quantify disability. Adding to the complexity, the definition of a healthy state can differ across studies due to inconsistent operational parameters. For example, categorizing all individuals with severe disabilities as equally disabled overlooks the nuances between mild, moderate, and severe disabilities.

The self-rated health instrument is often perceived as a more subjective evaluative method for gauging an individual's overall health status in contrast with other measures. While self-rated health is widely used for its simplicity, interpreting its results requires caution. This stems from its reliance on individuals to gauge their own physiological and psychological wellness. However, factors such as geographical locale, ethnicity, and cultural heritage can shape how respondents perceive their health, leading more toward a generalized health assessment rather than a specific one (*7*). This presents a potential hazard of underestimating the true condition of health.

In closing, the varying definitions of a healthy state and the assessment tools employed can yield different HSEs (*3*). Establishing a standard definition of a healthy state and adopting universal health state metrics is essential to enhance consistency and facilitate the comparison of study outcomes.

Health-Adjusted Life Expectancy

Compared to HSE indices, the HALE indicator is more attuned to population mortality rates and the fluctuating prevalence and severity of diseases, thereby affording a more all-encompassing evaluation of population health. The HALE indicator cluster incorporates health statuses from many dimensions in a weighted manner, yielding a more comprehensive and logical appraisal than single-dimensional assessments. However, collecting comprehensive data on each health dimension is challenging, especially given the absence of a standardized approach to weights adjustment. The HALE indicators that are most frequently utilized are the DALE and the QALE (*8*–*9*).

The comparability of HSE indicators, derived from self-reported health, is hindered by discrepancies across countries in survey methodologies and cultural differences in health reporting. Nonetheless, this challenge is significantly mitigated by the implementation of the DALYs measure (*10*). The DALY approach enables the computation of the HALE, otherwise recognized as the DALE. This method determines the estimated number of years an individual is projected to live in optimal health (*10*).

Utilizing the QALE has a distinct advantage as it can readily calculate the HALE for small-scale regions such as districts, cities, or provinces (*3*). This particular attribute enhances the value of QALE in evaluating the burden associated with behavioral risk factors, health determinants, diseases, and injuries (*9*). QALE achieves this by designating varying weighting factors to diverse disability states, effectively translating the survival time of these states into an equivalent survival time in an ideal healthy state, contingent on their corresponding weighting factors. As such, by measuring both the duration and quality of life expectancy, QALE offers a more holistic representation of the population's overall health status.

This study acknowledges two significant limitations. First, health is a multidimensional concept encompassing a broad spectrum of terms to characterize its varying dimensions. Consequently, our search strategy might not have encapsulated all pertinent studies. Second, our review is confined to studies published in English, thus potentially precluding valuable research available in other languages.

CONCLUSION

Our review has determined that a wealth of research exists on multiple aspects of HLE. Scholars have intensively examined and implemented related concepts, theoretical frameworks, and measurement procedures. Studies concentrating on older populations commonly use HSE indicators, whereas those incorporating the entire or adult population frequently employ HALE indicators. The majority of these studies adopt self-report questionnaires to evaluate a single domain. The DFLE has garnered significant attention among the HSE indicators, with ADL and IADL emerging as favored instruments for health state evaluation. The insights gleaned from this review can guide the creation of an all-encompassing healthy life expectancy system that includes multiple dimensions.

Conflicts of interest: No conflicts of interest.

Funding: Supported by the National Key Research and Development Program of China (2022YFC 2602301).

doi: 10.46234/ccdcw2023.186

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Submitted: July 05, 2023; Accepted: October 10, 2023

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Notifiable Infectious Diseases Reports

Reported Cases and Deaths of National Notifiable Infectious Diseases — China, August 2023*

Diseases	Cases	Deaths
Plague	4	1
Cholera	8	0
SARS-CoV	0	0
Acquired immune deficiency syndrome†	5,122	1,890
Hepatitis	166,606	190
Hepatitis A	1,111	0
Hepatitis B	138,875	22
Hepatitis C	23,214	167
Hepatitis D	21	0
Hepatitis E	2,618	1
Other hepatitis	767	0
Poliomyelitis	0	0
Human infection with H5N1 virus	0	0
Measles	105	0
Epidemic hemorrhagic fever	240	0
Rabies	12	8
Japanese encephalitis	80	1
Dengue	4,198	0
Anthrax	123	0
Dysentery	4,626	0
Tuberculosis	66,563	303
Typhoid fever and paratyphoid fever	678	0
Meningococcal meningitis	6	0
Pertussis	4,793	1
Diphtheria	0	0
Neonatal tetanus	2	0
Scarlet fever	1,209	0
Brucellosis	8,354	0
Gonorrhea	10,924	0
Syphilis	61,068	3
Leptospirosis	57	0
Schistosomiasis	1	0
Malaria	234	2
Human infection with H7N9 virus	0	0
Influenza	60,530	0
Mumps	7919	0
Rubella	103	0

Continued

Diseases	Cases	Deaths
Acute hemorrhagic conjunctivitis	12,742	0
Leprosy	23	0
Typhus	217	0
Kala azar	26	1
Echinococcosis	352	0
Filariasis	0	0
Infectious diarrhea[§]	125,319	0
Hand, foot and mouth disease	193,538	0
Total	735,782	2,400

* According to the National Bureau of Disease Control and Prevention, not included coronavirus disease 2019 (COVID-19).
† The number of deaths of acquired immune deficiency syndrome (AIDS) is the number of all-cause deaths reported in the month by cumulative reported AIDS patients.
§ Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever.
The number of cases and cause-specific deaths refer to data recorded in National Notifiable Disease Reporting System in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in the Chinese mainland are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan, China are not included. Monthly statistics are calculated without annual verification, which were usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via National Notifiable Disease Reporting System according to information verification or field investigations by local CDCs.

doi: 10.46234/ccdcw2023.179

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. 5 No. 44 Nov. 3, 2023

Published since November, 2019

Responsible Authority
National Health Commission of the People's Republic of China

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

Printing
Beijing Kexin Printing Co., Ltd

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