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Cost-effectiveness of universal genetic screening for familial hypercholesterolemia in young adults aged 18–40 years in China

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Abstract

Background Mortality from familial hypercholesterolemia (FH) remains high due to late diagnosis, and the rate of timely diagnosis remains low (< 10% globally and < 1% in China). Early screening and treatment could significantly reduce mortality risk, especially among young adults. This study aims to evaluate the cost-effectiveness of universal genetic screening of young adults aged 18–40 years compared to universal cholesterol screening or current passive screening strategies (opportunistic cholesterol screening and genetic cascade testing) for FH in China.

Methods A decision-analytic Markov model was constructed to simulate the lifetime (until 100 years old or 99% of patients died) coronary heart disease (CHD) events, discounted costs, gains in quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) of different screening strategies. The model targeted the general population aged 18–40 years (226,869,800 males and 209,030,180 females) from a healthcare provider's perspective. Model parameters were derived from published literatures and the largest nationwide screening program of FH in China. The willingness-to-pay threshold (US$38,042) was chosen as three times the Chinese per-capita gross domestic product (GDP) in 2023. Sensitivity analyses and threshold analyses were conducted to assess the robustness of the results.

Results Universal genetic screening of young adults aged 18–40 years is cost-effective when compared to both current passive screening strategies and universal cholesterol screening. Compared with current passive screening, universal genetic screening could prevent 172,956 CHD events (88,766 non-fatal, 84,191 fatal) with additional costs of US$40.45 billion and gaining additional 1.23 million QALYs, corresponding to an ICER of US$32,960/QALY gained. Implementing universal genetic screening at younger ages would reduce the ICER from US$36,901/QALY to US$28,910/QALY. The model was most sensitive to the cost and sensitivity of genetic testing. If the cost of genetic testing decreased from US$96.50 to US$38.83 or $2.76, universal genetic screening would become very cost-effective or even cost-saving.

Conclusions Universal FH genetic screening in young adults has the potential to be cost-effective in China, compared to current passive screening strategy and universal cholesterol screening strategy. Performing screening in younger age would result in better cost-effectiveness benefit.

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Keywords Cost-effectiveness, Familial hypercholesterolemia, Universal screening, Genetic testing, Opportunistic cholesterol screening

Background

Familial hypercholesterolemia (FH) is a well-established autosomal co-dominantly genetic disorder associated with elevated plasma low-density lipoprotein cholesterol (LDL-C) levels throughout life, which can cause premature coronary heart disease (CHD) [1, 2]. The disorder includes heterozygous FH (HeFH), homozygous FH (HoFH, very rare), compound HeFH, and double HeFH. The prevalence of HeFH in the global population ranges from 0.20 to 0.50% [2, 3], affecting approximately 1 per million individuals [4]. A recent population-based epidemiological study conducted in mainland China revealed that the overall HeFH prevalence in the general population aged 35–75 years was 0.13% [5], with a CHD proportion of 10.5%, five times higher than that (2.1%) in the general population [6]. Among untreated HeFH patients, the risk of CHD is estimated to be 50% for males by age 50 years old and 30% for females by age 60 years old [7, 8]. FH can pose a significant mortality risk, with a 10-year CHD mortality rate of 1.2% for those without a prior history of CHD and 10.7% for those with a history of CHD [9]. FH causes an annual medical expenditure of US$17,000 per person worldwide [10, 11]. Lifestyle modifications and statin-based cholesterol-lowering therapies can significantly reduce LDL-C levels and decrease the risk of CHD by 76% [12]. However, currently only 10% of FH patients worldwide can be diagnosed timely, and this fraction is even < 1% in the Asia–Pacific region, such as China [1, 13]. Among diagnosed FH patients, only 18.1% received lipid-lowering medications in China [5]. Improving the diagnosis and treatment rate of FH is essential to reduce CHD mortality.

In 2018, the World Heart Federation and the FH Foundation updated 11 recommendations about FH management to improve FH diagnosis, screening, and treatment worldwide [13]. Opportunistic screening detects community cholesterol in primary healthcare services and is the most commonly used FH screening approach in many countries, including China [14]. Cascade screening in relatives of confirmed patients is suggested by most of published FH management guidelines. However, due to poor awareness and implementation of current guidelines, opportunistic cholesterol screening and cascade screening strategies may miss > 90% of individuals living with FH [15–17]. In contrast, universal screening has been considered a potential alternative screening approach. Long-term statin trials have shown that young individuals treated with FH exhibited later risk events than affected parents with delay on statin therapy [18]. Universal screening for FH in young adults and children are gradually becoming more popular in many countries and regions, such as Australia (for 1–2-year-olds) [15], South Korea (for ≥ 21-year-olds and younger with family history of cardiovascular disease (CVD) or serious dyslipidemia) [19], the USA and Hong Kong (for < 20-year-olds) [20, 21], and Slovenia (for preschool children aged 5–6) [22].

Previous cost-effectiveness analyses of FH screening have largely focused on cascade screening [23–26]. A few studies on universal screening have demonstrated the potential economic advantages of universal cholesterol screening or universal genetic screening. However, these studies were all conducted in developed countries, and there are no economic evaluations of FH screening in low- and middle-income countries [14, 27–29]. China has screened 1 million general population in the pilot project Patient-centred Evaluative Assessment of Cardiac Events (PEACE) and detected 1383 FH individuals [5]. This suggests about 2 million individuals are living with FH in China's 1.4 billion population. Universal genetic or cholesterol screening for FH may help diagnose more FH patients and reduce FH disease burden, but its cost-effectiveness remains unknown in China.

By comparing with universal cholesterol screening and current passive screening approaches (opportunistic cholesterol screening and genetic cascade screening), this study aims to evaluate the cost-effectiveness of universal genetic screening in China for young adults aged 18–40 years with decision-tree Markov model. It will provide health economics evidence for health policy-making of FH screening program in China.

Methods

Study design

We conducted a model-based economic evaluation to assess the cost-effectiveness of three different screening strategies for HeFH (FH for short below) among young adults aged 18–40 years [14] in China: (1) universal genetic screening, (2) universal cholesterol screening (cholesterol screening followed by genetic confirmation diagnosis), and (3) current passive screening (opportunistic cholesterol screening and genetic cascade testing) from the healthcare provider's perspective. The model was constructed using Excel 2019, and we reported our analysis based on the Consolidated Health Economic

Evaluation Reporting Standards 2022 (CHEERS 2022) statement (Additional file 1: Table S1) [30].

Modeling

A decision tree model combined with a Markov model (Fig. 1) was constructed to estimate the lifetime costs and health outcomes of different screening strategies. We modeled the general population aged 18–40 years (226,869,800 male and 209,030,180 female) and their age distribution was derived from *China population census yearbook 2020* (Additional file 1: Table S2) [31]. The model simulated lifetime horizon until 99% of patients died or the patients reached 100 years old [32]. We calculated that there were 306,546 male and 282,442 female FH patients aged 18–40 years, based on the combined FH prevalence of 0.14% from the largest nationwide screening program of FH in China and a cohort study conducted in nine provinces (see Additional file 1 for details) [5, 33]. The Markov model was run with 1-year cycle length, based on previous cost-effectiveness analysis models of FH screening and the slow progression of CVD [14, 23, 24]. Three health states were included: (1) alive without CHD, (2) alive with CHD, and (3) dead. All individuals entered the Markov model with a starting health status of "alive without CHD." Within each cycle, a certain proportion of patients could experience a non-fatal CHD event (e.g., non-fatal myocardial infarction, unstable angina, or other non-fatal acute coronary syndromes), a fatal CHD event (any death directly attributable to coronary heart disease), or death from a non-CHD cause. Patients in the "alive without CHD" state could suffer a non-fatal CHD event and transition to the "alive with CHD" state, remain in the original state, or suffer a fatal CHD event or non-CHD-related death and transition to the "dead" state. Patients in the "alive with CHD" state may not experience any event and stay in the original state, experience another non-fatal CHD event and remain in the original state, or experience a fatal CHD event or non-CHD-related death and transition to the "dead" state.

Data analysis

The states transition probabilities were derived from published cohort studies (Table 1) (Additional file 1: Table S3) [12, 34–37]. To account for the increased risk of CHD recurrence in individuals with FH, the age- and sex-related standardized mortality ratios (SMR) was applied (Additional file 1: Table S4) [37, 38]. The non-CHD-related death (age and sex specific) was calculated by the natural mortality of general Chinese population minus the CHD-related death of general Chinese population, which were obtained from *China population census yearbook 2020* and *China Health Statistics Yearbook 2022*, respectively (Additional file 1: Tables S5–S9) [31, 39]. The proportion of detected FH patients receiving lipid-lowering treatment (statins) was 88.8%, while for undetected patients, it was 13.8% (see Additional file 1 for details) [5, 40]. In addition, the risk reduction (76%) of CHD onset was used to capture the efficacy of statin treatment, which was obtained from a famous

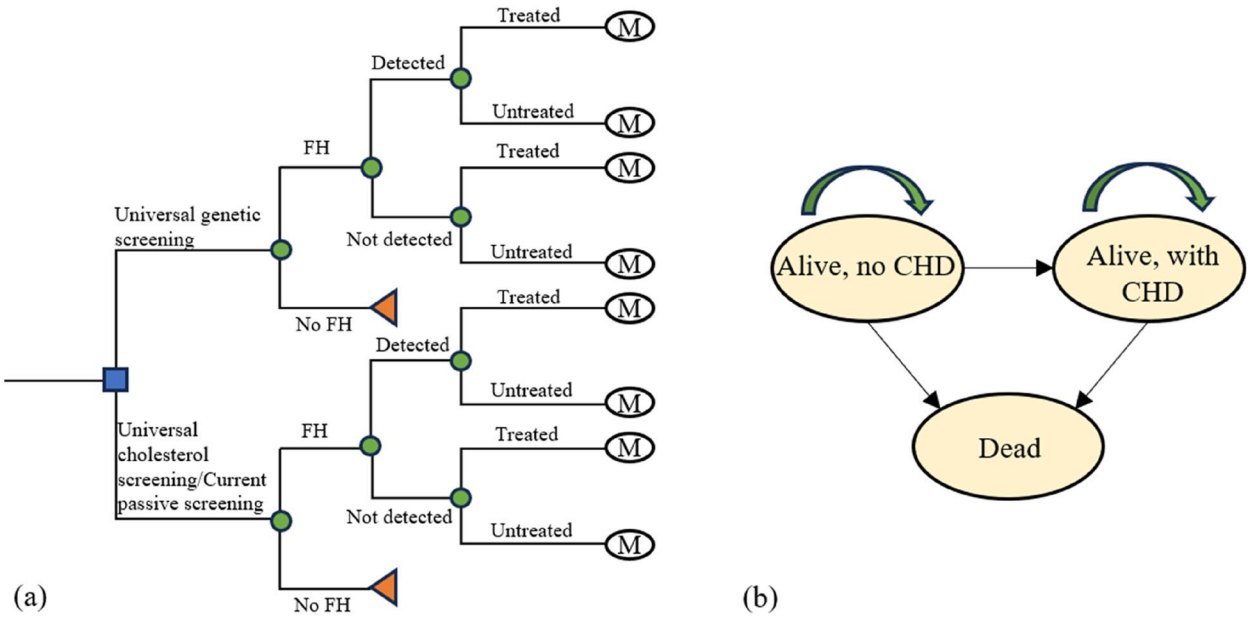


Fig. 1 Decision-analytic Markov model structure. **a** Decision tree model structure. **b** Markov model structure. CHD, coronary heart disease; FH, familial hypercholesterolemia

Table 1 Model inputs

Parameter	Base-case	Range	Distribution	Reference
Prevalence and detecting rate				
FH prevalence	0.0014	0.0012–0.004	Fixed	[5, 33]
Proportion of FH individuals detected in the passive screening cohort	0.01	0–0.1	Fixed	[1, 2]
Sensitivity of genetic test for primary screening	0.9323	0.45–1	Fixed	[14, 24, 27, 42–48]
Sensitivity of genetic test for patients with lipid abnormalities	1	0.9–1	Fixed	[49]
Sensitivity of lipid test for primary screening	0.48	0.43–0.54	Fixed	[45, 50]
Treatment rate				
Proportion of diagnosed patients treated in both groups	0.88	0.6–1	Fixed	[40]
Proportion of undiagnosed patients treated in both groups	0.138	0.138–0.647	Fixed	[5]
Treatment adherence	0.638	0.579–1	Fixed	[41]
Transition probability				
"Alive, with not CHD" health state				
Risk of any CHD among general population (age-specific)	Table S3	–	–	[34]
HR of CVD risk for FH patients compared to the general population	2.03	1.17–3.51	Fixed	[33]
Proportion of fatal CHD	0.234	0.187–0.280	Log-normal (0.129, 0.010)	[35, 36]
HR of statin treatment	0.24	0.180–0.300	Log-normal (0.240, 0.031)	[12]
"Alive, with CHD" health state				
Recurrent risk of non-fatal CHD	0.0137	0.011–0.142	Log-normal (0.014, 0.001)	[37]
Recurrent risk of fatal CHD	0.0158	0.013–0.043	Log-normal (0.016, 0.001)	[37]
Cost (US$)				
Genetic test	96.50	48.25–144.75	Gamma (15.37, 6.28)	[54]
Cholesterol test	5.52	2.70–9.93	Gamma (8.94, 0.617)	Calculated[a]
Acute event costs				
Non-fatal CHD	6854.54	5618.06–8091.14	Gamma (118.05, 60.88)	[55, 56]
Fatal CHD	8898.45	7800.48–9996.42	Gamma (252.31, 36.98)	[55, 56]
Non-CHD death	1561.29	1249.04–5676.40	Gamma (1.91, 856.63)	[39]
Proportion of death out of hospital	0.50	0–1	Beta (1.42, 1.42)	[7]
Chronic costs (annually)				
Post-CHD (year 1)	3264.84	2611.87–3917.81	Gamma (96.04, 33.99)	[55, 57, 58]
Post-CHD (year 2 +)	2867.29	2293.83–3440.75	Gamma (96.04, 29.86)	[55, 57, 58]
Statin treatment	256.25	128.12–307.50	Gamma (31.36, 8.17)	Calculated[b]
Utilities				
"Alive without CHD" health state (age- and sex-specific)	Table S10	–	–	[51]
Utility decrement of acute CHD event for males	−0.086	−0.095 to −0.077	Beta (351.04, 3730.78)	[52, 53]
Utility decrement of acute CHD event for females	−0.089	−0.098 to −0.080	Beta (349.88, 3581.36)	[52, 53]
"Alive, with CHD" health state				
Utility decrement of "alive with CHD" for males	−0.053	−0.058 to −0.048	Beta (363.75, 6499.40)	[52, 53]
Utility decrement of "alive with CHD" for females	−0.042	0.046 to −0.038	Beta (367.98, 8393.52)	[52, 53]
Discount	0.05	0–0.08	Fixed	[32]

CHD Coronary heart disease, *FH* Familial hypercholesterolemia, *HR* Hazard ratio, *CVD* Cardiovascular disease

[a] The average price of medical services of 27 provinces

[b] Calculated based on the average annual cost of medication and sales volume composition ratios of the six statins marketed in China (atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin, fluvastatin)

cohort study of Dutch FH patients (see Additional file 1 for details) [12]. Adherence to lipid-lowering therapies was 63.8% [41]. For universal genetic screening group, the sensitivity of genetic testing as a primary screening method among general population was estimated to be 93.23% (range: 45–100%), based on the median value from 10 studies [14, 24, 27, 42–48]. For universal cholesterol screening group, the sensitivity of lipid screening as a primary method was set at 48% [49]. Given that genetic testing is considered the gold standard for FH

diagnosis, the sensitivity for confirming FH in patients with lipid abnormalities using genetic testing was set at 100%, according to published studies (Table 1) [45, 50]. The screening coverage of current passive screening group was 1% from Consensus Statement of the European Atherosclerosis Society in Asia–Pacific region [1, 2].

The age- and sex-related utilities of individuals in the "alive without CHD" state was obtained from a Chinese survey using EQ-5D-5L (Additional file 1: Table S10) [51]. The utility decrements associated with post-CHD (alive with CHD) and recurrence of non-fatal CHD events were derived from published cross-sectional study on health-related quality of life among Chinese CHD patients (Additional file 1: Table S11) [52, 53]. The utilities were discounted by 5% annually [32].

Based on healthcare system perspective, we included only direct medical costs comprised screening costs, acute event costs, chronic post-CHD management costs, and statin treatment costs. For screening costs, the cost of FH genetic testing in China was US$96.50 per individual [54], while the mean cost of cholesterol screening, derived from the 2023 medical service prices across 27 provinces and cities in China, was US$5.52 per person. The acute event costs comprised fatal CHD (US$8898.45), non-fatal CHD (US$6854.54), and non-CHD-related death (US$1561.29) [39, 55, 56]. The annual post-CHD management costs were divided into the first year (US$3264.84) and second year onward (US$2867.29) [55, 57, 58]. These costs were derived from published economic burden studies and public websites (see Additional file 1 for details). All costs were presented in 2023 US dollars (1 RMB = 0.14191 USD). The costs were also discounted by 5% annually [32].

The model was simulated independently for every age (18–40 years), and the costs and health outcomes were calculated to capture the total cohort outcomes of three FH screening scenarios, which included the number of fatal and non-fatal CHD events, total costs, quality-adjusted life years (QALYs), life years (LYs), and incremental cost-effectiveness ratios (ICERs) (Fig. 2). The primary outcome was the ICER, which was defined as the incremental cost per QALY gained. To evaluate a strategy's cost-effectiveness, we used WHO standards [30] and a willingness-to-pay (WTP) threshold of US$12,681 to US$38,042 (one to three times the gross domestic product (GDP) per capita in China in 2023) per QALY gained. Strategies with an ICER < 1, 1–3, and > 3 times the per capita GDP were denoted as very cost-effective, cost-effective, and not cost-effective, respectively. All detailed parameters and data are shown in Additional file 1.

Model validation

Our model parameters and outputs were validated to align with the current literature and real-world data. The number of people who needed to be screened for FH in the general population aged 18–40 to prevent one CHD event was compared with the Australian study [12], and the number for the general population aged 20 was compared with the US study [59].

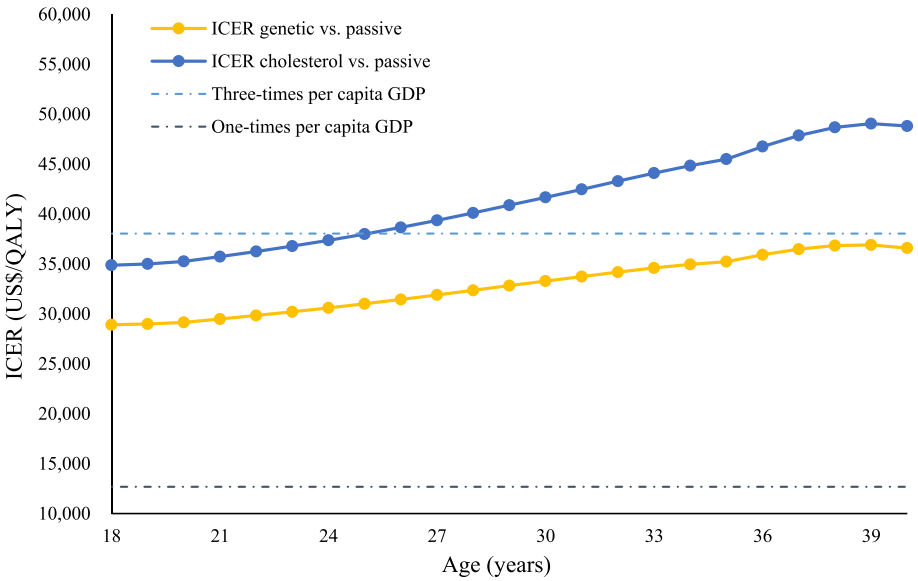


Fig. 2 The ICER for each age within the 18–40 years age range. QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

Subgroup analysis

We performed subgroup analysis for urban and rural areas (Additional file 1: Tables S7 and S8) and the subgroup differences in ICER between urban and rural populations were compared based on their distinct epidemiological characteristics (see Additional file 1 for details) [31, 60, 61].

Sensitivity analysis and threshold analysis

We conducted one-way sensitivity analysis (OWSA) within a predetermined range of uncertainty derived from the literature or an assumed range (see Additional file 1 for details), as demonstrated in the tornado diagram (Fig. 3).

We also performed probabilistic sensitivity analysis (PSA) based on the values sampled from the distributions of model parameters. The results of 1000 Monte Carlo simulations were plotted using ICER scatterplot, and a cost-effectiveness acceptability curve (CEAC) was derived to determine the proportion of simulations based on which screening strategy was cost-effective over its comparators across a range of WTP thresholds (Fig. 4).

The threshold analysis was performed to capture the critical values of important parameters corresponding to ICERs at one and three times the GDP per capita. We chose the four most sensitive and meaningful parameters to perform threshold analysis based on the results of OWSA (Fig. 5).

Results

Cost-effectiveness of universal genetic screening

Compared to current passive screening, universal genetic screening of young adults aged 18–40 years would prevent 172,956 CHD events (88,766 non-fatal, 84,191 fatal) over a lifetime (Table 2), which was more costly (US$50.95 billion vs. US$10.50 billion) but yielded more QALYs (8,946,949 vs. 7,719,658) and LYs (9,461,368 vs. 8,193,640). The number needed to screen to prevent one CHD event was 2495 and the ICER was US$32,960/QALY, which was below three-times per capita GDP (US$38,253/QALY), indicating that universal genetic screening was cost-effective. In contrast, while universal cholesterol screening yielded more QALYs (8,249,570 vs. 7,719,658) compared to the current passive screening, it was not cost-effective due to its higher cost associated with cholesterol screening and genetic confirmation diagnosis (US$22.60 billion), resulting in an ICER of US$41,398/QALY, which exceeded three times the per capita GDP (Table 2).

Performing universal genetic screening at each age between 18 and 40 years old was all cost-effective compared to the current passive screening (Fig. 2), with the ICER between US$28,910/QALY and US$36,901/QALY (Additional file 1: Table S12, Fig. S1). Although universal cholesterol screening was generally not cost-effective compared to the current passive screening, it showed a cost-effectiveness advantage in young adults aged 18–25, with the ICER ranging between US$34,873/QALY and US$37,992/QALY (Fig. 2, Additional file 1: Table S13, Fig. S1). Conducting universal genetic or cholesterol screening in younger age resulted in more significant cost-effectiveness advantage (Fig. 2).

Comparison of rural and urban differences

When conducting the cost-effectiveness evaluation of FH screening for urban and rural populations separately, universal genetic screening demonstrated greater cost-effectiveness than current universal cholesterol screening and passive screening in both subgroups. In the urban subgroup, the ICERs were US$11,801/QALY and US$15,055/QALY, respectively, while in the rural subgroup, the ICERs were US$9693/QALY and US$12,473/QALY, respectively. The higher prevalence of FH in rural areas resulted in greater cost-effectiveness of universal genetic screening in rural populations compared to urban populations (Additional file 1: Tables S14 and S15).

Sensitivity analysis and cost-effectiveness acceptability curve

When comparing universal genetic screening with the current passive screening, OWSA showed that ICER was most sensitive to sensitivity of genetic screening (Fig. 3a, Additional file 1: Table S16). Specifically, altering this sensitivity within the range of 45 to 100% resulted in a variation in the ICER estimates, ranging from US$29,613/QALY to US$84,317/QALY (Additional file 1: Table S16). ICER was next most sensitive to the discount rate for costs and outcomes, the cost of genetic testing, the coverage of statin treatment for diagnosed patients from universal screening, FH prevalence, the coverage of statin treatment for undiagnosed patients in both groups, and the hazard ratio (HR) of CVD risk for FH patients compared to the general population (Fig. 3a). The results suggested that variation in most of parameters within their ranges did not affect the cost-effectiveness of universal genetic screening and the model was robust.

When comparing universal cholesterol screening with the current passive screening, the OWSA results indicated that the most sensitive parameters were similar as those for universal genetic screening. Additionally, when most parameters fluctuated within their ranges, the conclusion that universal cholesterol screening was not cost-effective compared to the current passive screening remains robust (Fig. 3b, Additional file 1: Table S17).

The ICER scatterplot of the PSA (Fig. 4a) demonstrated that for universal genetic screening compared

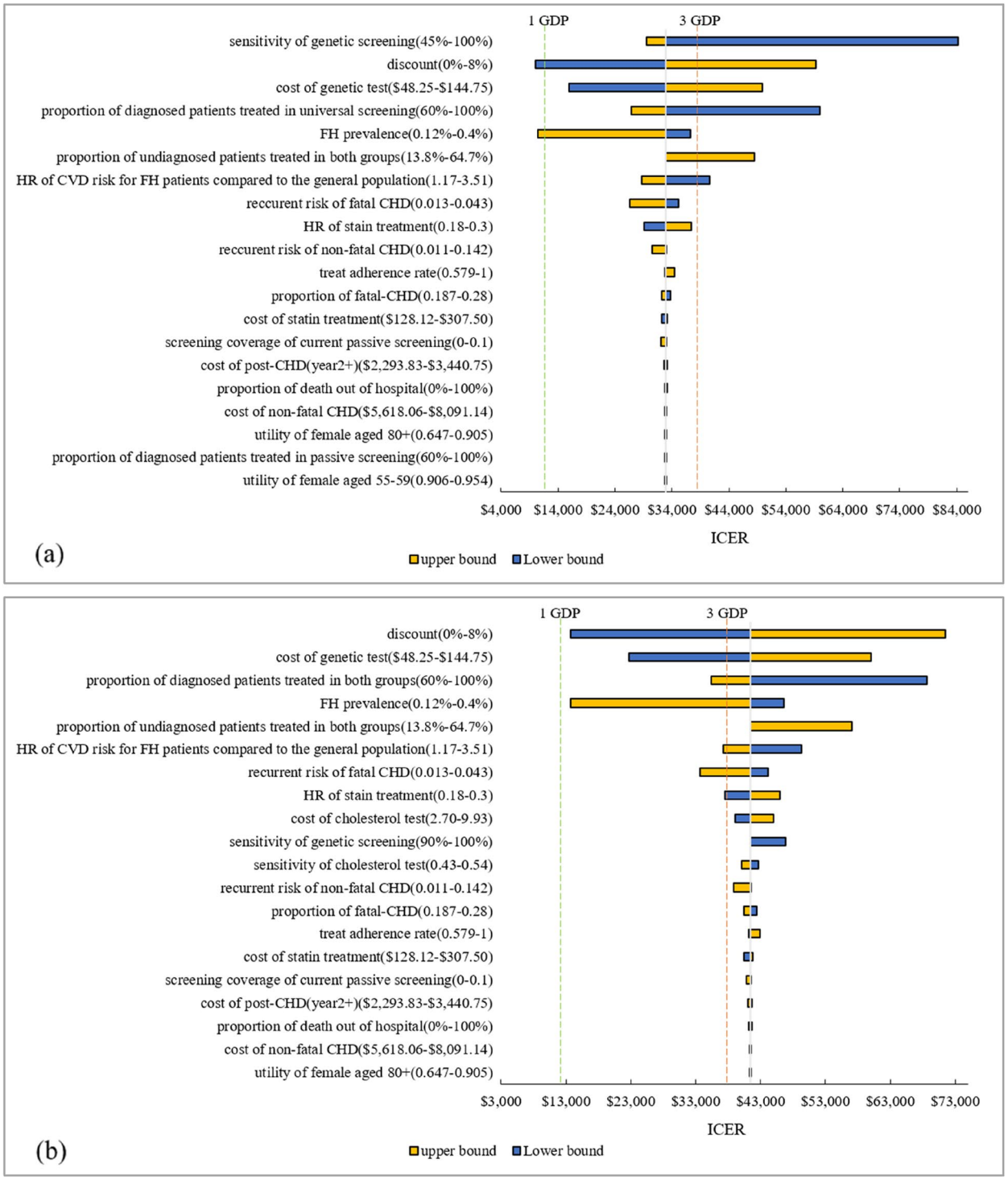
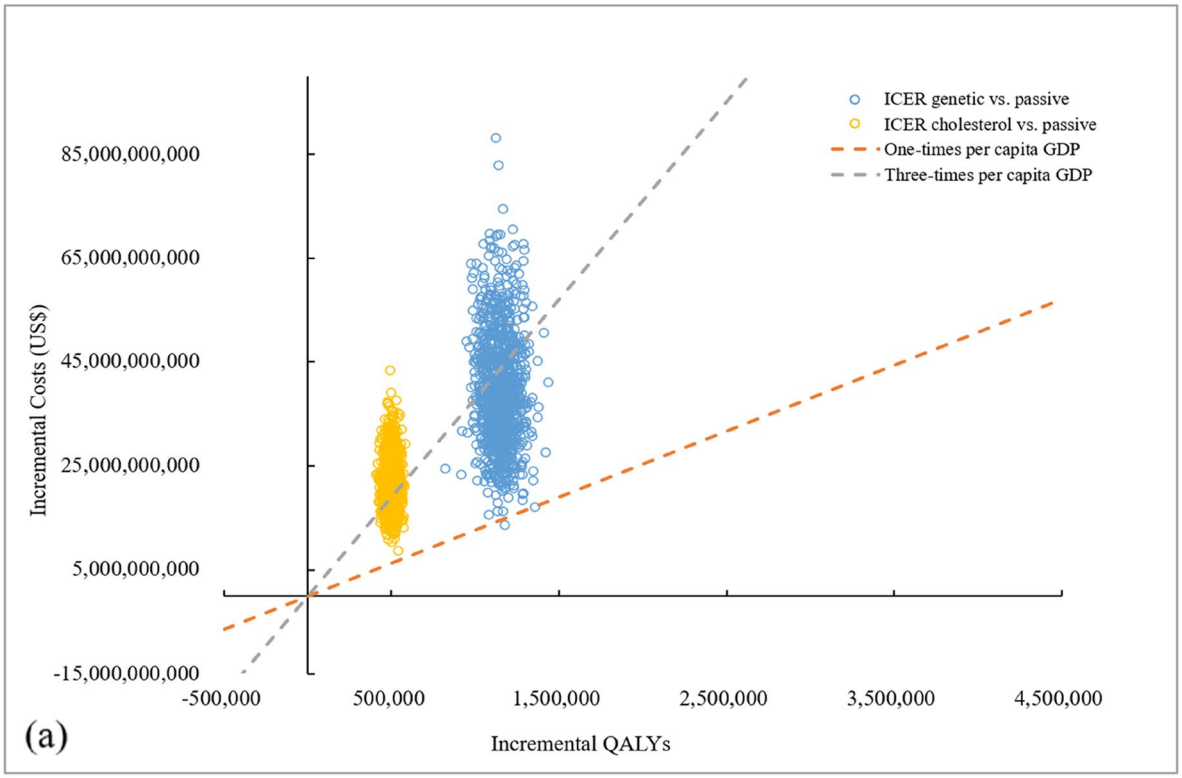


Fig. 3 Tornado diagram of one-way sensitivity analysis. **a** Tornado diagram of one-way sensitivity analysis for ICER of universal genetic screening for young adults aged 18–40 years, compared with current passive screening strategies; **b** tornado diagram of one-way sensitivity analysis for ICER of universal cholesterol screening for young adults aged 18–40 years, compared with current passive screening strategies. CHD, coronary heart disease; FH, familial hypercholesterolemia; CVD, cardiovascular disease; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio



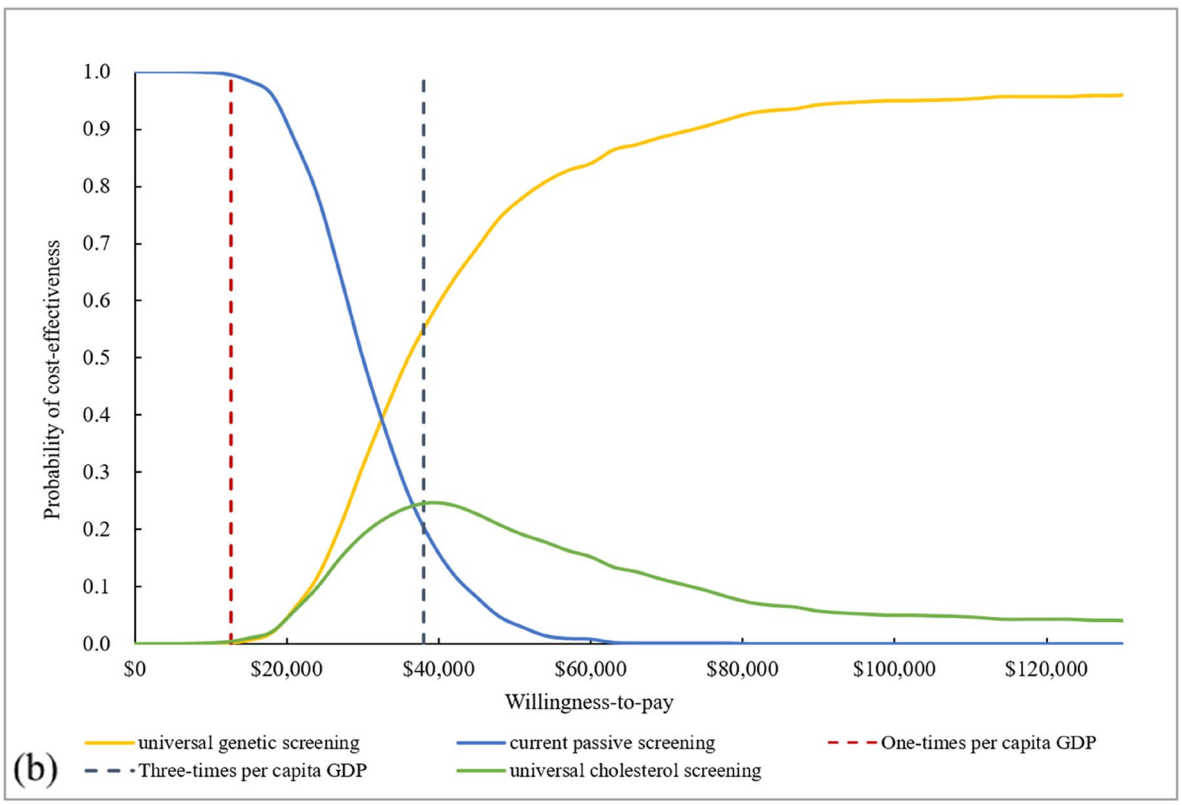


Fig. 4 Probabilistic sensitivity analysis results. **a** ICER scatterplot of 1000 Monte Carlo simulation; **b** Cost-effectiveness acceptability curve of universal genetic screening vs. current passive screening strategies vs. universal cholesterol screening. QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

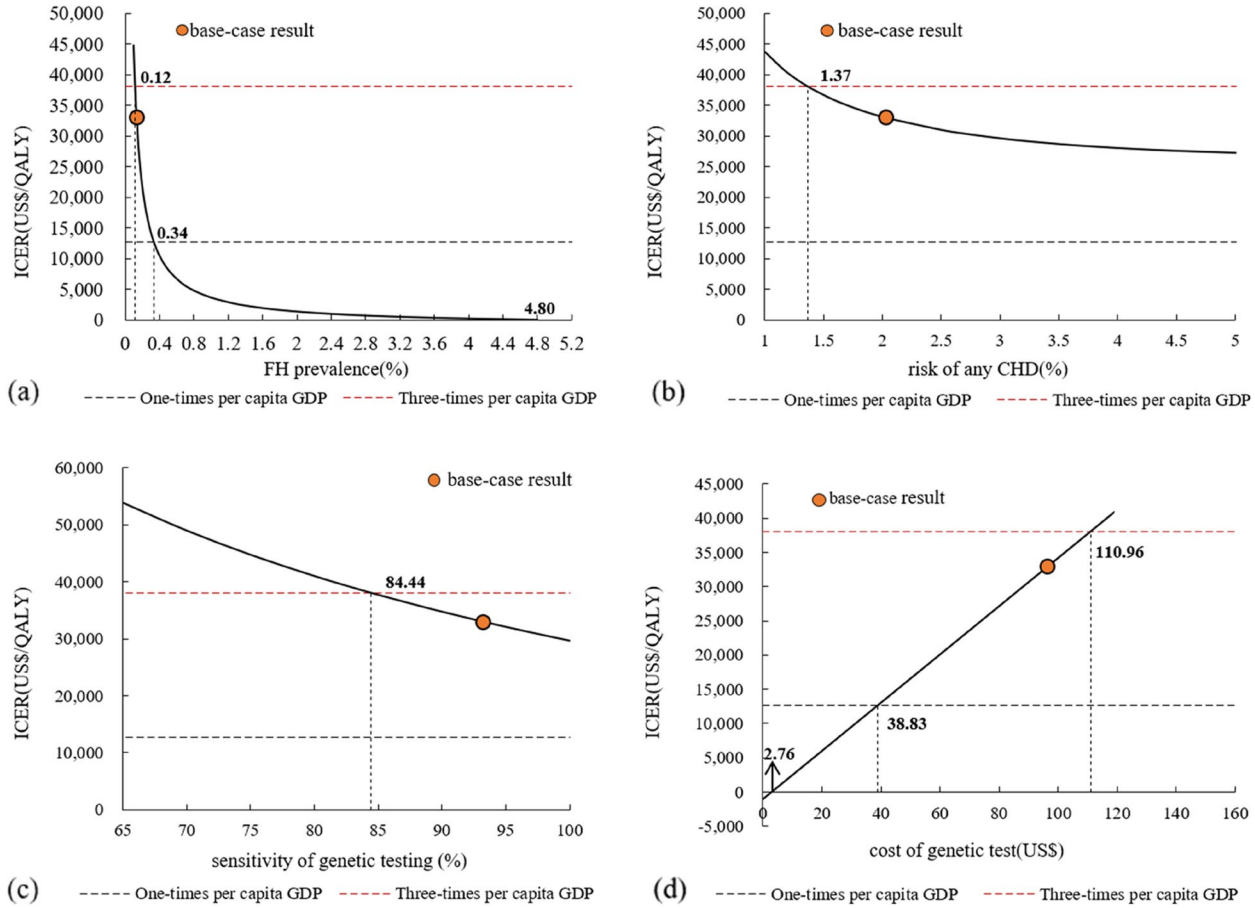


Fig. 5 Threshold analysis for universal genetic screening compared to current passive screening. **a** FH prevalence; **b** risk of any CHD; **c** sensitivity of genetic testing; **d** cost of genetic testing. FH, familial hypercholesterolemia; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; GDP, gross domestic product

to the current passive screening, over 50% of the ICERs were below three times the per capita GDP of China. In contrast, for universal cholesterol screening compared to the current passive screening, over 50% of the ICERs were above three times the per capita GDP of China. The CEAC (Fig. 4b) indicated that when the WTP was below US$32,600/QALY, the current passive screening had the highest probability of being cost-effective among the three screening strategies. When the WTP exceeded US$32,600/QALY, universal genetic screening had the highest probability of being cost-effective, while universal cholesterol screening consistently had the lowest probability of being cost-effective. The results of PSA verified the robustness of the base-case analysis results.

Impact of FH prevalence and HR of CVD risk

Higher FH prevalence leads to lower ICER. If the FH prevalence was less than 0.12%, the ICER would exceed 3-times per-capita GDP and thus universal genetic screening was not cost-effective. If the FH prevalence was greater than 0.34%, universal genetic screening would become very cost-effective, and if the FH prevalence exceed 4.80%, universal genetic screening would become cost-saving (Fig. 5a).

Higher HR of CVD risk for FH patients compared to the general population leads to lower ICER. If the HR of CVD risk was less than 1.37, the ICER would exceed 3-times per-capita GDP and thus universal genetic screening was not cost-effective (Fig. 5b).

Impact of costs and sensitivity of genetic screening

Lower sensitivity of genetic testing leads to higher ICER. If the sensitivity of genetic testing was less than 84.44%, the ICER would exceed 3-times per-capita GDP and thus universal genetic screening was not cost-effective (Fig. 5c).

Lower cost of genetic testing leads to lower ICER. If the cost of genetic was greater than US$110.96, the ICER would exceed 3-times per-capita GDP and thus universal genetic screening was not cost-effective. If the cost of

Table 2 Lifetime results of base-case analysis

Outcome	Current passive screening	Universal cholesterol screening	Universal genetic screening	Difference between universal cholesterol screening and current passive screening	Difference between universal genetic screening and current passive screening
Not-fatal CHD	692,586	662,541	603,821	−30,046	−88,766
Fatal CHD	423,415	393,122	339,224	−30,293	−84,191
Total CHD events	1,116,001	1,055,663	943,045	−60,339	−172,956
Number needed to screen	4,359,000	435,899,980	435,899,980	431,540,980	431,540,980
Number needed to screen to prevent one CHD event	–	–	–	7152	2495
Total LYs	8,193,640	8,741,433	9,461,368	547,793	1,267,728
Total QALYs	7,719,658	8,249,570	8,946,949	529,912	1,227,292
Screening costs (US$)	444,707,418	22,597,552,805	42,063,824,990	22,152,845,387	41,619,117,572
Acute event costs (US$)	2,984,385,478	2,531,027,048	1,905,310,714	−453,358,430	−1,079,074,764
Chronic management costs (US$)	6,245,480,021	5,524,675,673	4,371,956,478	−720,804,348	−1,873,523,543
Treatment costs (US$)	823,802,224	1,782,461,717	2,608,322,896	958,659,492	1,784,520,671
Total costs (US$)	10,498,375,141	32,435,717,242	50,949,415,077	21,937,342,101	40,451,039,936
ICER (US$/LY)	–	–	–	40,047 (25,790–65,777)[a]	31,908 (18,196–54,812)[a]
ICER (US$/QALY)	–	–	–	41,398 (26,387–66,916)[a]	32,960 (18,612–57,037)[a]

CHD Coronary heart disease, *QALYs* Quality-adjusted life years, *Lys* Life years, *ICER* Incremental cost-effectiveness ratio

[a] 95% confidence interval

genetic testing was less than US$38.83, universal genetic screening would become very cost-effective. Additionally, if the cost was less than US$2.76, universal genetic screening would become cost-saving (Fig. 5d).

Discussion

The main findings of the present study of FH screening were as follows: universal genetic screening for FH in the general population aged 18–40 years in China was more cost-effective compared to the current passive screening strategy (ICER: US$32,960/QALY) and universal cholesterol screening, and conducting universal screening in younger age groups would yield better cost-effectiveness outcomes. Moreover, when considering the epidemiological differences between urban and rural areas, universal genetic screening exhibited superior cost-effectiveness compared to the overall population in both settings, with a more pronounced cost-effectiveness advantage observed in rural areas than in urban areas. The model was most sensitive to the sensitivity and cost of genetic screening.

Published studies suggest that universal FH screening for young individuals is likely to be cost-effective in developed countries [14, 27–29]. McKay et al. found that universal cholesterol screening followed by diagnostic genetic testing at age 1–2 years combined with cascade testing was cost-effective in the UK and the ICER was £12,480/QALY gained [27]. Marks et al. showed that universal cholesterol screening of 16-year-olds and cascade screening by cholesterol of family members yielded similar costs (£2777 versus £3097) per life year gained in the UK [28]. Marquina et al. demonstrated that the ICER of universal genetic screening of young adults aged 18–40 years was AU$27,705/QALY gained, which would be cost-effective in Australia, compared to opportunistic cholesterol screening and genetic cascade testing [14]. Guzauskas et al. indicated that universal genetic screening for FH would likely to be cost-effective in US adults between 20 and 40 years old with an ICER US$72,000–89,400/QALY gained [29]. This study is the first to assess the cost-effectiveness of universal FH genetic screening for young adults in China. Compared to published cost-effectiveness analyses of universal screening [14, 27–29], our research comprehensively evaluates the economic feasibility of both active and passive screening methods currently available, and conducts age-specific simulations for the general population aged 18–40, making it a valuable contribution to the field of FH screening and treatment.

Our OWSA results show that the parameter with the most significant impact on the ICER is the sensitivity of genetic testing. Currently, genetic testing techniques can identify common FH mutation genotypes (e.g., LDLR, APOB, or PCSK9 genes) and are unable to detect other rare gene mutations. Therefore, when it is used as a primary screening method, its sensitivity may not reach

100% among the general population [43]. For this parameter, we selected the median value (93.23%) reported in ten studies as the base-case value and set a range of 45 to 100% in the sensitivity analysis to capture the reality. Threshold analysis indicates that when the sensitivity of genetic testing exceeds 84.44%, universal genetic screening begins to demonstrate a cost-effectiveness advantage. As the sensitivity increases, the economic advantage of universal genetic screening becomes more pronounced. When sensitivity is set to 100%, the ICER of universal genetic screening compared to current passive screening is US$29,613/QALY, which is close to the US$27,705/QALY in Australia [14].

Our study shows that the cost of genetic testing plays a crucial role in determining the cost-effectiveness of universal genetic or cholesterol screening. For universal genetic screening, if the current testing costs can be reduced from the baseline of US$96.50 to US$38.83, the ICER would decrease to below one time the GDP per capita (US$12,681/QALY), making universal genetic screening highly cost-effective in China. For universal cholesterol screening, since genetic testing is still required to confirm FH after the initial screening of LDL-C, the overall costs, even with the lower price of lipid testing, remain high due to the additional expense of genetic testing. This offsets the improvements in CHD events and QALYs gained from universal cholesterol screening, making it not cost-effective compared to the current passive screening approach. Universal cholesterol screening would begin to show economic advantages only if the cost of genetic testing is reduced to US$87.82 or lower. Given China's large population, the cost of performing population-based genetic or cholesterol FH screening for all individuals aged 18–40 years would be approximately US$50.95 billion and US$32.44 billion, respectively, placing a substantial burden on medical insurance funds and healthcare systems. Therefore, the cost of genetic testing needs to be further reduced before implementing universal screening.

Our study demonstrates that the cost-effectiveness of universal genetic screening is affected by the FH prevalence, and a higher prevalence would result in a greater benefit from universal genetic screening. Given that the LDL-C level of FH individuals was lower in China (6.9 ± 1.7 mmol/L) than in Western population (9.96 ± 0.04 mmol/L), the number of FH patients in China may be underestimated based on Western country's Simon Broome (SB) and Dutch Lipid Clinic Network (DLCN) diagnose criteria [62]. Therefore, based on Chinese expert consensus on diagnosis of FH (CEFH) criteria, the 0.14% FH prevalence of China was derived as the base-case value [5]. Although this parameter was based on the best available evidence, we still varied it in sensitivity analysis with the global FH prevalence of 0.4% as the upper limit (ICER decreased to US$10,503/QALY for universal genetic screening). Our threshold analysis result suggests that if the FH prevalence in a country was lower than 0.12%, universal genetic screening would not be cost-effective. This indicates that universal genetic screening should be prioritized for settings with high FH prevalence.

Our results reveal that the ICER is sensitive to the coverage of statin treatment for both diagnosed and undiagnosed FH patients across three groups. As the treatment coverage for undiagnosed FH patients (who receive statins following a cardiovascular event) increases, the cost-effectiveness of the current passive screening strategy gradually improves and eventually surpasses that of universal genetic screening. This highlights that it is important to enhance the coverage of statin treatment in decreasing the disease and economic burden of FH, regardless of whether universal screening is implemented or not. Despite the availability of clinical guidelines for FH detection and treatment, their implementation remains poor in many countries, including China [13], resulting in low awareness of FH among the general public and medical community. Further, only 18.1% of FH individuals receive lipid-lowering medication in China, which is far less than in other countries [63], and none of the treated FH patients achieves their LDL-C targets [5]. Thus, increasing treatment coverage and reaching treatment effect size should be a priority in the limited budget.

Our study demonstrates that universal genetic screening for FH is cost-effective for young adults among both urban and rural areas. However, implementing universal screening in China faces several practical feasibility challenges, including low participation due to limited awareness and cultural barriers, particularly in rural areas with limited access to healthcare services and medical facilities. Additionally, significant financial support is needed for genetic testing, healthcare infrastructure development, and professional training. China has launched a nationwide breast cancer and cervical cancer screening program, which provides valuable experience for the implementation of universal screening, including in rural areas [64]. Given the practical limitations of universal screening, we recommend prioritizing universal genetic screening for younger age groups. Moreover, integrating universal genetic screening with existing cancer screening programs or targeting high-risk groups could help reduce costs and improve feasibility. Finally, as studies suggest the potential cost-effectiveness of combining genetic screening with reverse cascade screening [27, 28], we recommend further research to validate this approach in China.

Our study has several potential limitations. First, genetic screening is still developing and there exists limited data on the cost of genetic screening. We searched literatures and found one available price in China as base-case analysis, and we conducted extensive sensitivity analysis in the cost of genetic testing to validate the robustness of the base-case analysis results. We also performed the threshold analysis to find the critical threshold of this cost which make the universal genetic screening very cost-effective or cost-saving. Second, although our subgroup analysis compared the ICER based on the epidemiological differences between urban and rural areas and demonstrated its cost-effectiveness, further empirical studies are needed to validate these cost-effectiveness findings given the actual infrastructure and economic constraints in rural areas. Third, although false positives (non-pathogenic variants) were not considered in the model due to their extremely rare occurrence (high specificity > 99%), we accounted for them by incorporating a 20% upward adjustment for statin therapy costs in the sensitivity analysis. The robust results indicated that false positives did not significantly impact the outcomes. Fourth, our results were robust to parameter uncertainty, but the estimates of results may be affected by future changes in the cost of screening due to more advanced genetic screening technologies and the potential impact of medication treatment on the disease-related parameters. Finally, potential legal, ethical, and societal issues associated with universal genetic screening, including insurance implications and the potential for genetic discrimination, need to be fully assessed in the real-world. Despite these limitations, our study provides insights into the feasibility of universal genetic FH screening of young adults.

Conclusions

Our model suggests that performing universal genetic screening for FH in young adults aged 18–40 years in China has the potential to be cost-effective from healthcare provider's perspective, compared to current passive screening strategy and universal cholesterol screening strategy. Performing screening in younger age would result in better cost-effectiveness benefit. Our findings require further empirical research to validate.

Abbreviations

FH	Familial hypercholesterolemia
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
CHD	Coronary heart disease
LDL-C	Low-density lipoprotein cholesterol
ICERs	Incremental cost-effectiveness ratios
QALYs	Quality-adjusted life years
PEACE	Patient-centred Evaluative Assessment of Cardiac Events
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
SMR	Standardized mortality ratio
LYs	Life years
GDP	Gross domestic product
WTP	Willingness-to-pay
OWSA	One-way sensitivity analysis
PSA	Probabilistic sensitivity analysis
CEAC	Cost-effectiveness acceptability curve
HR	Hazard ratio
CVD	Cardiovascular disease
DLCN	Dutch Lipid Clinic Network
SB	Simon Broome
CEFH	Chinese expert consensus on diagnosis of FH

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03966-7.

Additional file 1: Tables S1–S17. Figure S1. Table S1 CHEERS checklist. Table S2 The number of the general population and estimated FH patient. Table S3 Age-specific CVD risk. Table S4 Standardized mortality ratios of FH. Table S5 Non-CHD-related death of FH patients. Table S6 Natural mortality of general population. Table S7 The number of the general population in urban and rural areas. Table S8 Natural mortality of general population in urban and rural areas. Table S9 CHD-related death of general population. Table S10 The age- and sex-related utilities of "alive without CHD" state. Table S11 The age- and sex-related utilities of "alive with CHD" state. Table S12 Base-case results of each age (genetic vs. passive). Table S13 Base-case results of each age (cholesterol vs. passive). Table S14 Lifetime results of the base-case analysis of urban population. Table S15 Lifetime results of the base-case analysis of rural population. Table S16 Lifetime results of one-way sensitivity analysis (genetic vs. passive). Table S17 Lifetime results of one-way sensitivity analysis (cholesterol vs. passive). Fig. S1 Incremental cost-effectiveness ratio of each age

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Not applicable.

Authors' contributions

MS and RM conceived and designed the study. RM and FS collected the data, analysed the data, and carried out the analysis. RM wrote the first draft of the manuscript. BZ, CL, JW, and LS edited the manuscript. MS and LZ critically revised the manuscript. All the authors contributed to writing the paper and agreed with the manuscript results and conclusions. All authors read and approved the final manuscript.

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Data availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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