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·临床研究·

老年人群全口缺牙与心血管疾病发生风险的回顾性队列研究

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【摘要】　目的　探讨老年人群基线全口缺牙状态与新发心血管疾病（CVD）风险的相关性，并验证该关联在不同临床亚组中的一致性与结果稳健性，为老年人群CVD早期风险识别和综合防控提供依据。**方法**　基于中国健康与养老追踪调查（CHARLS）和美国健康与退休研究（HRS）两项纵向队列公开数据开展回顾性分析，纳入年龄≥60岁且基线无CVD病史者。以基线全口缺牙为暴露变量，随访期间新发CVD事件为结局变量。采用Kaplan-Meier法分析组间CVD无事件生存概率差异。通过多因素Cox比例风险回归模型评估全口缺牙与CVD发生风险的独立关联，同时采用区间删失比例风险模型作为敏感性分析，以评价事件时间近似处理对风险估计结果的影响。以风险比及95%置信区间进行描述。开展年龄、性别、教育等六维度亚组分析与交互作用检验以验证结果普适性，并采用五项敏感性分析验证可靠性。**结果**　CHARLS与HRS队列分别纳入5 522及7 738例研究参与者。生存分析显示两队列中全口缺牙组CVD无事件生存概率均显著低于非全口缺牙组（$P < 0.001$）。完全调整模型提示全口缺牙是老年人新发CVD的独立危险因素（CHARLS：$HR = 2.64$，95% CI：2.33~2.99，$P < 0.001$；HRS：$HR = 2.69$，95% CI：2.46~2.95，$P < 0.001$），区间删失模型验证结果与传统Cox模型高度一致。该关联在六维度各亚组中普遍存在，交互作用P值均>0.05。五项敏感性分析结果与主分析一致，提示结果稳健性良好，并且以中风为单独结局时其关联最强（CHARLS：$HR = 2.85$；HRS：$HR = 2.91$）。**结论**　中美两项队列一致显示，全口缺牙可独立增加老年人CVD风险，该关联在不同亚组中保持一致且稳健，提示全口缺牙可作为老年人群CVD风险评估的补充指标。

【关键词】　老年人群；　全口缺牙；　心血管疾病；　中国健康与养老追踪调查；　美国健康与退休研究；　纵向队列；　回顾性分析；　Cox比例风险回归
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Association between complete edentulism and incident cardiovascular disease among older adults: a retrospective cohort study

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【Abstract】　Objective　To explore the association between baseline complete edentulism and the risk of incident cardiovascular disease (CVD) in older adults, and to verify the consistency across clinical subgroups and robustness of the findings, providing evidence for early CVD risk identification and comprehensive prevention and management among older adults. **Methods**　Data were derived for a retrospective analysis from two longitudinal cohorts: the China Health and Retirement Longitudinal Study (CHARLS) and the Health and Retirement Study (HRS). Participants aged ≥ 60 years without prevalent CVD at baseline were enrolled. Baseline complete edentulism was defined as the exposure variable, and incident CVD during follow-up was set as the outcome variable. Kaplan - Meier analysis was performed to

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compare differences in CVD-free survival probability between groups. Multivariable Cox proportional hazards regression models were used to estimate the independent association between edentulism and incident CVD. In addition, an interval-censored proportional hazards model was applied as a sensitivity analysis to assess the potential impact of approximating event times on the risk estimates. Hazard ratios and 95% confidence intervals were used for description. Six-dimension subgroup (age, sex, education, etc.) analyses and interaction tests were performed to confirm the generalizability of the association, and five sensitivity analyses were conducted to validate the reliability of the results. **Results** A total of 5 522 participants from the CHARLS and 7 738 participants from the HRS were included. Survival analysis revealed that the CVD-free survival probability was significantly lower in the complete edentulism group than in the non-edentulous group across both cohorts ($P < 0.001$). Fully adjusted regression models identified complete edentulism as an independent risk factor for new-onset CVD among older adults (CHARLS: *HR* = 2.64, 95% *CI*: 2.33 – 2.99, $P < 0.001$; HRS: *HR* = 2.69, 95% *CI*: 2.46 – 2.95, $P < 0.001$). The results from the interval-censored model were highly consistent with those from the conventional Cox model. This association persisted across all predefined six dimensions subgroups with all interaction $P > 0.05$. Outcomes of five sensitivity analyses were consistent with primary analyses, indicating favorable robustness. The strongest association was observed when stroke was treated as a separate endpoint (CHARLS: *HR* = 2.85; HRS: *HR* = 2.91). **Conclusion** Findings from both the Chinese and U.S. cohorts consistently indicate that complete edentulism independently elevates the risk of incident CVD in older adults, with robust associations across diverse subgroups. Complete edentulism may serve as an auxiliary indicator for CVD risk stratification among older adults.

【Key words】 aged population; complete edentulism; cardiovascular diseases; China Health and Retirement Longitudinal Study; Health and Retirement Study; longitudinal cohort; retrospective analysis; Cox proportional hazards regression

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心血管疾病(cardiovascular disease,CVD)是全球导致老年人群死亡和残疾的首要病因,其高发病率和高致死率持续加重公共卫生负担[1-2]。尽管高血压、糖尿病等传统危险因素已被广泛纳入现行CVD风险防控体系,但受多病共存和功能衰退等叠加因素影响,老年人群残余风险仍然突出,亟须发掘简易、可推广、低成本的预警指标[3-4]。口腔健康与心血管之间的关联日益受到关注,口腔慢性炎症和牙周疾病可通过持续性低度炎症、病原体血行播散及内皮功能损伤等途径参与动脉粥样硬化和心脑血管事件的发生发展[5]。全口缺牙作为口腔病变的终末状态,其病因涵盖重度牙周病、多发龋病、外伤及医疗可及性等多重因素,是长期口腔疾病负担与社会经济因素共同作用的综合表征[6-7],其更能直观反映个体持续性口腔健康损害,具有作为CVD风险补充指标的潜在价值。既往多数队列研究与Meta分析提示缺牙与CVD风险升高相关,但针对全口缺牙的独立验证证据有限[8-10],仍存在研究人群相对单一、跨国家验证不足、暴露定义及混杂因素控制不一致等局限,该关联在不同人群和亚组中的稳定性尚不明确。基于此,本研究依托中美两项大规模纵向队列,即中国健康与养老追踪调查(China Health and Retirement Longitudinal Study, CHARLS)与美国健康与退休研究(Health and Retirement Study, HRS),开展回顾性分析,系统评估全口缺牙状态与新发CVD的关联,并通过亚组分析和多项敏感性分析检验一致性与稳健性,以期为口腔健康与CVD发病关联提供跨人群流行病学证据。

1　资料和方法

1.1　研究设计与数据来源

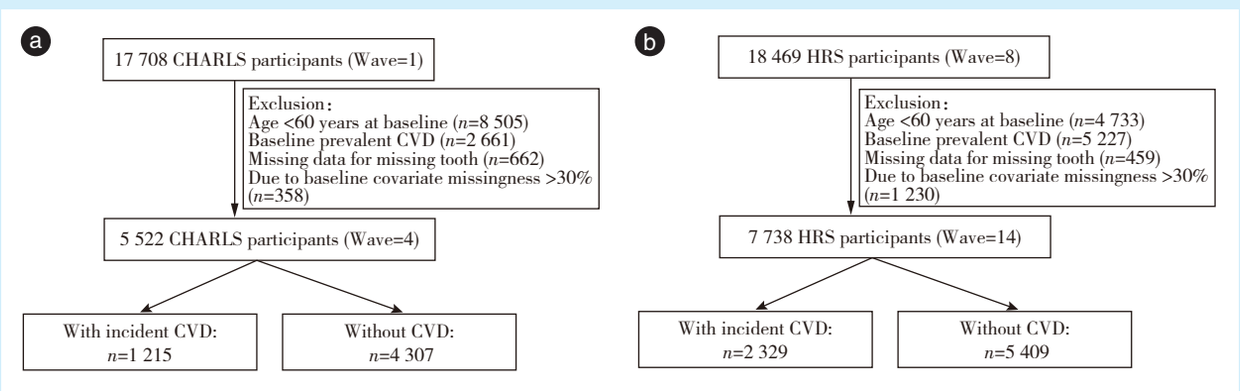
研究数据来源于两项具有国际代表性的大规模纵向调查:CHARLS(http://charls.pku.edu.cn)[11-12]和HRS(https://hrs.isr.umich.edu)[13]。CHARLS已获北京大学生物医学伦理委员会批准(批准号:IRB00001052-11015),HRS已获密歇根大学机构审查委员会批准(批准号:HUM00061128)。本研究遵循赫尔辛基宣言原则进行,报告参照观察性研究报告规范(Strengthening the Reporting of Observational Studies in Epidemiology, STROBE)指南。本研究为基于公开数据库的二次分析研究,仅使用去标识化的公开数据,不涉及受试者直接接触或身份识别信息。因此,根据相关伦理规范,

本研究无需额外伦理审批。

1.2　研究人群

CHARLS队列基线为2011年(Wave 1),纳入17 708例参与者,随访终点为2017年(Wave 4),共包含4个波次(2011、2013、2015、2017),观察期约为7年。HRS队列以2006年(Wave 8)为本次分析基线,纳入18 469例参与者,随访终点为2018年(Wave 14),每2年随访1次。共包含7个波次(2006、2008、2010、2012、2014、2016、2018),观察期约为13年。但由于各参与者进入研究和发生事件的时间不同,实际随访时间存在个体差异。对于随访期间失访的参与者,以其末次完成随访的时间点作为删失时间进行处理。CHARLS从Wave 1至Wave 4的面板随访应答率约为86%;HRS各波次的横截面应答率均维持在85%~90%。最终纳入分析的参与者中,CHARLS平均随访2.61个波次,HRS平均随访3.10个波次。

两个队列均按以下标准进行排除:基线年龄小于60岁者、基线时已患CVD者、全口缺牙信息缺失者,以及基线协变量缺失比例超过30%者。最终CHARLS纳入5 522例参与者,HRS纳入7 738例参与者。CHARLS随访至第4波,HRS随访至第14波(图1)。对于纳入分析对象中缺失比例≤30%的协变量,采用多重插补法(multiple imputation)进行处理。具体采用链式方程多重插补(multiple imputation by chained equations,MICE)方法,生成5组插补数据集,插补模型纳入所有分析变量作为预测因子。各插补数据集分别进行统计建模后,采用Rubin规则合并估计结果。各变量的缺失情况详见表1"缺失数"列。此外,在敏感性分析中采用完整病例分析以评估缺失数据处理方式对结果的影响。



a: CHARLS research population screening flowchart; b: HRS research population screening flowchart; CHARLS: China Health and Retirement Longitudinal Study; HRS: Health and Retirement Study; CVD: cardiovascular disease; Wave: survey wave(data collection round)

Figure 1　Flowchart of screening the study population from the CHARLS and HRS datasets

图1　CHARLS与HRS数据库研究人群筛选流程图

1.3　暴露变量与结局变量

暴露变量为基线全口缺牙状态,基于各数据库中自报口腔健康调查模块定义(即受访时是否已失去全部牙齿),将参与者分为全口缺牙组与非全口缺牙组。结局变量为随访期间新发CVD事件,定义为首次发生心脏病或中风(以先发生者为准)。由于CHARLS和HRS均采用两年一次的随访设计,CVD事件通过受访者在随访波次中的自我报告获得,因此无法确定事件发生的精确日期,仅能确定其发生于最近一次无CVD状态随访时间与首次报告事件随访时间之间,即形成区间删失数据。CVD发生时间以基线至首次CVD事件报告的间隔年数计算;随访期间未发生CVD者则以末次随访时间进行删失处理。

1.4　协变量

协变量的选取基于既往文献中已知的CVD危险因素及缺牙的潜在混杂因素。人口学特征包括基线年龄(连续变量)、性别(男性/女性)、教育水平(低/中/高)、婚姻状况(已婚/未婚)和居住地(城镇/农村),其中教育水平根据受教育程度进行分类:低教育水平定义为小学及以下学历,中等教育水平定义为初中或高中学历,高教育水平定义为大专及以上学历。婚姻状况根据问卷中的婚姻状态变量重新分类,已婚包括已婚且配偶共同居住以

及同居状态，未婚包括从未结婚、分居、离异及丧偶。行为因素包括吸烟状况（是/否）和饮酒状况（是/否），吸烟状况根据当前吸烟状态定义，自报目前仍吸烟者归为当前吸烟组，从不吸烟及既往吸烟但已戒烟者归为非当前吸烟组。饮酒状况根据过去12个月内饮酒行为定义，过去12个月内有饮酒行为者归为当前饮酒组，否则归为非饮酒组。体格指标为体质指数（body mass index，BMI，kg/m^2），作为连续变量纳入分析。基线合并症包括高血压、糖尿病、癌症、慢性肺病和关节炎，均以二分类变量（是/否）纳入分析。所有协变量均根据CHARLS和HRS问卷中的原始条目进行定义。

1.5　样本量估算

本研究为基于已有公开数据库的二次分析研究，纳入CHARLS和HRS数据库中所有符合纳入与排除标准的参与者，样本量由数据可用性决定，而非基于预先的效应量假设进行计算。最终纳入13 260例参与者，随访期间共观察到3 544例新发CVD事件（CHARLS 1 215例，HRS 2 329例），事件发生率为26.7%。根据经验法则，Cox回归模型中每个协变量至少需要10~20个事件以保证估计的稳定性[14]，本研究模型3纳入13个协变量，所需最低事件数为130~260个，实际事件数远超此要求，表明样本量充足，能够保证统计效能。

1.6　偏倚控制

本研究针对可能影响结果有效性的主要偏倚采取了以下控制措施：①选择偏倚：通过严格的纳入与排除标准，排除基线已患CVD者以确保队列的同质性，排除基线协变量缺失比例>30%者以保证数据质量，并通过对两个独立队列的合并分析增强外部推广性；②混杂偏倚：通过构建递进调整的多变量Cox回归模型（模型1至模型3），逐步控制人口学特征、行为因素和合并症等已知混杂因素的影响；③反向因果偏倚、竞争风险偏倚及信息偏倚：通过多项敏感性分析进行评估。

1.7　统计学分析

基线特征的描述采用均数±标准差或中位数（上下四分位距）表示连续变量，分类变量以频数（百分比）表示。连续变量的正态性通过Shapiro-Wilk检验判定；组间比较采用Kruskal-Wallis检验（非正态连续变量）或卡方检验（分类变量）。

缺牙在不同人口学特征亚组中的分布通过计算各亚组缺牙患病率及其95%置信区间进行描述。CVD无事件生存概率的比较采用Kaplan-Meier法进行估计，组间差异通过log-rank检验进行评价。

采用Cox比例风险回归模型评估缺牙与CVD之间的关联，以风险比（hazard ratio，*HR*）及95% *CI*表示。主分析构建以下三个递进调整模型：模型1（未调整模型）：仅纳入暴露变量（全口缺牙），不调整任何协变量，以估计缺牙与心血管疾病复合结局之间的粗关联。模型2（社会人口学调整模型）：在模型1的基础上，进一步调整年龄、性别、教育水平、婚姻状况及居住地，以控制基本人口学特征对结局的混杂效应。模型3（全调整模型）：在模型2的基础上，进一步调整高血压、糖尿病、癌症、慢性肺病、关节炎、吸烟状态、饮酒状态及BMI，纳入全部协变量，以估计全口缺牙与心血管疾病复合结局之间的独立关联。

考虑到CVD事件发生时间来源于定期随访调查，实际发生时间存在区间不确定性，进一步采用区间删失比例风险模型进行验证分析，以评估事件时间近似处理对风险估计的影响。此外，为检验连续变量与Cox比例风险模型log hazard之间的线性关系，在进行Cox比例风险回归分析前采用限制性立方样条（restricted cubic spline，RCS）方法对年龄和BMI进行非线性检验。

所有检验均为双侧检验，$P < 0.05$为差异有统计学意义。统计分析在R软件（版本4.3）中完成，主要使用的R包包括survival（Cox回归与生存分析）、survminer（Kaplan-Meier曲线绘制）、icenReg（区间删失比例风险模型）、mice（多重插补）、forestploter（森林图绘制）、tableone（基线特征表构建）、cmprsk（竞争风险分析）、patchwork（图形拼接）及openxlsx（数据导出）。

1.8　亚组分析与敏感性分析

亚组分析在模型3的基础上，按年龄（<75岁/≥75岁，依据既往老年人群研究中高龄老年人的常用分层方式[15]）、性别（男性/女性）、教育水平（低/中及高）、吸烟状况（从不吸烟/曾吸烟）、糖尿病（是/否）和BMI（<25/≥25 kg/m^2，依据世界卫生组织超重定义标准[16]）进行分层，以评估缺牙与CVD关联在不同亚组中的一致性。各亚组分析中排除该分层变量本身作为调整协变量。亚组间效应修饰作用通过在Cox模型中加入缺牙与分层变量的乘积交互项，采用似然比检验评估交互作用*P*值。

为检验结果的稳健性，开展了以下敏感性分析：分别以心脏病和中风作为单独结局重新拟合模型3；排除基线后2年内发生CVD事件的参与者

以减少反向因果偏倚的影响；采用完整病例分析以评估缺失数据处理对结果的影响；采用Fine-Gray亚分布风险模型将非CVD死亡作为竞争事件进行竞争风险分析。

2　结　果

2.1　研究对象基线特征

本研究最终纳入13 260例老年研究对象，其中CHARLS队列5 522例，HRS队列7 738例。两组基线特征比较显示（表1），中美两国老年人群在人口学特征、生活方式及疾病负担方面存在明显差异（$P < 0.001$）。相较于美国HRS队列，中国CHARLS队列受试者整体更为年轻，且男性构成比例更高，但受教育程度普遍偏低，且以农村居住者为主，吸烟者比例更高，而饮酒者比例相对较低。HRS队列BMI更高，且高血压、糖尿病、关节炎及癌症的患病比例更高，而CHARLS队列中慢性肺病更为常见。核心暴露全口缺牙在两队列间分布均衡，其患病率分别为16.2%（CHARLS）和18.4%（HRS）

表1　中美两队列老年人群基线特征比较

Table 1　Comparison of baseline characteristics between older adults in the Chinese and USA cohorts　*n*(%)

Characteristic	Category	Overall (*n*=13 260)	CHARLS (*n*=5 522)	HRS (*n*=7 738)	Z/χ^2	*P*	Missing data
Age[*Median*(P_{25}, P_{75})]		68.00[64.00, 74.00]	66.00[62.00, 72.00]	69.00[65.00, 75.00]	18.62	<0.001	0(0)
Sex	Male	5 732 (43.2)	2 794 (50.6)	2 938 (38.0)	202.14	<0.001	0(0)
	Female	7 528 (56.8)	2 728 (49.4)	4 800 (62.0)			
Education level	Low	5 193 (39.2)	3 492 (63.2)	1 701 (22.0)	2308.47	<0.001	339(2.56)
	Medium	5 864 (44.2)	1 397 (25.3)	4 467 (57.7)			
	High	2 203 (16.6)	633 (11.5)	1 570 (20.3)			
Marital status	Married	9 081 (68.5)	4 164 (75.4)	4 917 (63.5)	205.83	<0.001	0(0)
	Unmarried	4 179 (31.5)	1 358 (24.6)	2 821 (36.5)			
BMI/(kg/m^2)[*Median*(P_{25}, P_{75})]		25.00[21.92, 28.50]	22.30[20.13, 24.85]	27.00[24.10, 30.50]	52.47	<0.001	3(0.02)
Smoking	No	10 659 (80.4)	3 780 (68.5)	6 879 (88.9)	852.36	<0.001	213(1.61)
	Yes	2 601 (19.6)	1 742 (31.5)	859 (11.1)			
Drinking	No	7 562 (57.0)	3 750 (67.9)	3 812 (49.3)	454.28	<0.001	42(0.32)
	Yes	5 698 (43.0)	1 772 (32.1)	3 926 (50.7)			
Complete edentulism	No	10 939 (82.5)	4 627 (83.8)	6 312 (81.6)	10.56	0.004	0(0)
	Yes	2 321 (17.5)	895 (16.2)	1 426 (18.4)			
Hypertension	No	7 576 (57.1)	3 976 (72.0)	3 600 (46.5)	856.72	<0.001	22(0.17)
	Yes	5 684 (42.9)	1 546 (28.0)	4 138 (53.5)			
Diabetes	No	11 684 (88.1)	5 205 (94.3)	6 479 (83.7)	313.58	<0.001	33(0.25)
	Yes	1 576 (11.9)	317 (5.7)	1 259 (16.3)			
Cancer	No	12 143 (91.6)	5 483 (99.3)	6 660 (86.1)	651.24	<0.001	19(0.14)
	Yes	1 117 (8.4)	39 (0.7)	1 078 (13.9)			
Chronic lung disease	No	12 131 (91.5)	4 866 (88.1)	7 265 (93.9)	137.42	<0.001	11(0.08)
	Yes	1 129 (8.5)	656 (11.9)	473 (6.1)			
Arthritis	No	6 796 (51.3)	3 611 (65.4)	3 185 (41.2)	760.38	<0.001	9(0.07)
	Yes	6 464 (48.7)	1 911 (34.6)	4 553 (58.8)			
Residence	Urban	7 285 (54.9)	1 975 (35.8)	5 310 (68.6)	1 392.56	<0.001	0(0)
	Rural	5 975 (45.1)	3 547 (64.2)	2 428 (31.4)			

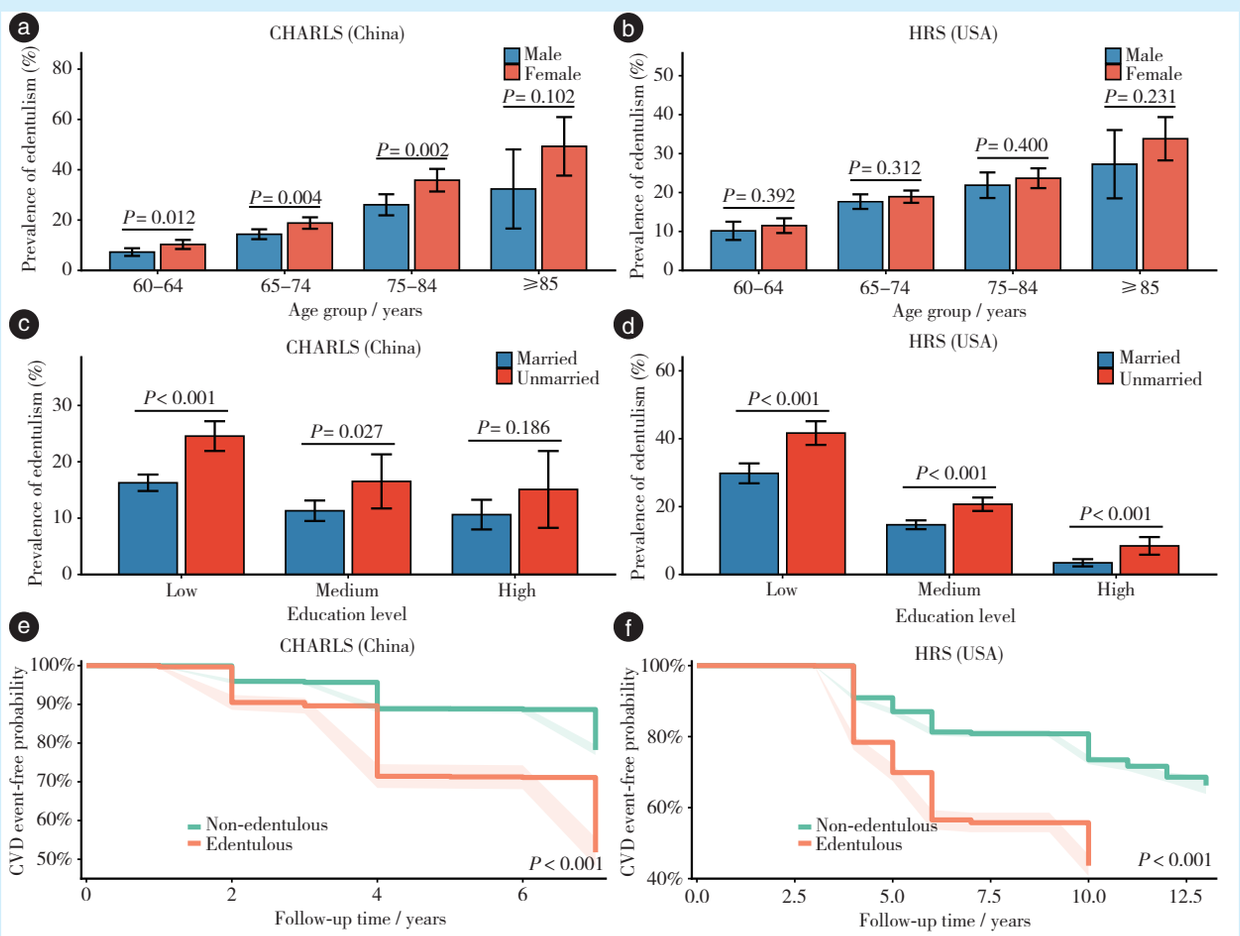
Continuous variables were compared using the Wilcoxon rank-sum test (*Z* values reported); categorical variables were compared using the chi-square test (χ^2 values reported). Missing date values were calculated based on the final analytic sample (n = 13 260); Missing counts represent the original missing status of each variable prior to multiple imputation; after imputation, all 13 260 participants were included in the final analysis models. CHARLS: China Health and Retirement Longitudinal Study; HRS: Health and Retirement Study; BMI: body mass index

2.2　两队列基线全口缺牙分布特征与CVD无事件生存分析

按年龄与性别分层的分析显示（图2a、2b），CHARLS和HRS队列中，全口缺牙患病率均随年龄增长而明显升高，且各年龄组中女性全口缺牙率均高于男性。

按教育水平与婚姻状况分层(图2c、2d),两队列均呈现出教育水平越低,全口缺牙患病率越高的梯度分布。在不同教育水平内,未婚者的全口缺牙率明显高于已婚者。以上提示全口缺牙在高龄、女性、低教育水平及未婚人群中更为常见。

随访期间,CHARLS和HRS队列中全口缺牙组CVD事件发生比例明显高于非全口缺牙组,并且具有更高的CVD累积发病率和发病密度(表2)。Kaplan-Meier生存分析显示(图2e、2f,表2),在随访终点时,CHARLS队列非全口缺牙组CVD无事件生存概率为78.22%(95% *CI*:76.91%~79.54%),全口缺牙组为51.79%(95% *CI*:48.25%~55.59%);HRS队列非全口缺牙组为66.23%(95% *CI*:63.86%~68.69%),全口缺牙组为27.79%(95% *CI*:21.63%~35.70%)。两队列中全口缺牙组CVD无事件生存概率均显著低于非全口缺牙组(Log-rank检验$P<0.001$),且全口缺牙组下降速度明显更快,提示在中美两国老年人群中全口缺牙与CVD发病风险升高存在正向关联。



a: distribution of edentulism prevalence stratified by age group and sex in the CHARLS cohort; b: distribution of edentulism prevalence stratified by age group and sex in the HRS cohort; c: distribution of edentulism prevalence stratified by education level and marital status in the CHARLS cohort; d: distribution of edentulism prevalence stratified by education level and marital status in the HRS cohort. Error bars represent 95% *CI*. e: Kaplan-Meier CVD-free survival curves stratified by edentulism status in the CHARLS cohort. f: Kaplan-Meier CVD-free survival curves stratified by edentulism status in the HRS cohort. The chi-square test was used for comparisons between groups of categorical variables. Survival curves were compared using two-sided log-rank tests. Sample sizes: CHARLS, n = 5 522; HRS, n = 7 738. CHARLS: China Health and Retirement Longitudinal Study; HRS: Health and Retirement Study; CVD: cardiovascular disease

Figure 2　Distribution of baseline complete edentulism and cardiovascular disease event-free survival analysis in the two cohorts

图2　两队列基线全口缺牙分布特征与心血管疾病无事件生存分析

表2　两队列随访期间心血管疾病事件发生情况

Table 2　Cardiovascular disease event incidence results during follow-up in the two cohorts

Characteristics	CHARLS (*n*=5 522)		HRS (*n*=7 738)	
	Without complete edentulism (*n*=4 627)	Complete edentulism (*n*=895)	Without complete edentulism (*n*=6 312)	Complete edentulism (*n*=1 426)
Number of CVD events	849	366	1 574	755
Cumulative incidence (%)	18.35	40.89	24.94	52.95
Person-years of follow-up	26 500	4 632	53 062	10 012
Incidence density (/1 000 person-years)	32.04	79.02	29.66	75.41
CVD-free survival probability(%, 95% *CI*)	78.22 (76.91–79.54)	51.79 (48.25–55.59)	66.23 (63.86–68.69)	27.79 (21.63–35.70)

CHARLS: China Health and Retirement Longitudinal Study; HRS: Health and Retirement Study; CVD: cardiovascular disease

2.3　全口缺牙与CVD发生风险的Cox回归分析及区间删失模型验证

Cox比例风险回归分析显示，在未调整模型中（模型1），CHARLS队列 *HR* = 2.69（95% *CI*：2.38~3.04），HRS队列 *HR* = 2.78（95% *CI*：2.55~3.04）。进一步调整人口学特征后（模型2），该关联依然保持稳定。完全调整模型（模型3）中CHARLS队列 *HR* = 2.64（95% *CI*：2.33~2.99），HRS队列 *HR* = 2.69（95% *CI*：2.46~2.95）。区间删失比例风险模型结果显示，区间删失模型所得效应估计与传统Cox模型高度一致。在完全调整模型中，CHARLS队列 *HR*=2.68（95% *CI*：2.36~3.04），HRS队列 *HR*=2.73（95% *CI*：2.49~3.00）（图3）。

上述结果提示全口缺牙与新发CVD风险升高存在显著的独立关联（$P < 0.001$），是老年人群新发CVD的独立危险因素。将首次事件报告时间作为近似事件时间未明显影响全口缺牙与CVD风险关联的估计。

2.4　全口缺牙与CVD发生风险的亚组分析

亚组分析结果显示（图4），CHARLS与HRS队列中全口缺牙与新发CVD的正向关联在各亚组均保持一致，所有交互作用 *P* 值均>0.05。在CHARLS队列，总体 *HR* = 2.64（95% *CI*：2.33~2.99），各亚组 *HR* 均>2.4，仅糖尿病亚组关联 *HR* = 1.65（95% *CI*：0.96~2.83）。HRS队列总体 *HR* = 2.69（95% *CI*：2.46~2.95），各分层亚组 *HR* 均在2.43~2.81之间。结果提示全口缺牙与CVD风险升高的关联不受年龄、性别、教育水平等因素的明显影响，具有良好的普适性。

2.5　全口缺牙与CVD发生风险的敏感性分析

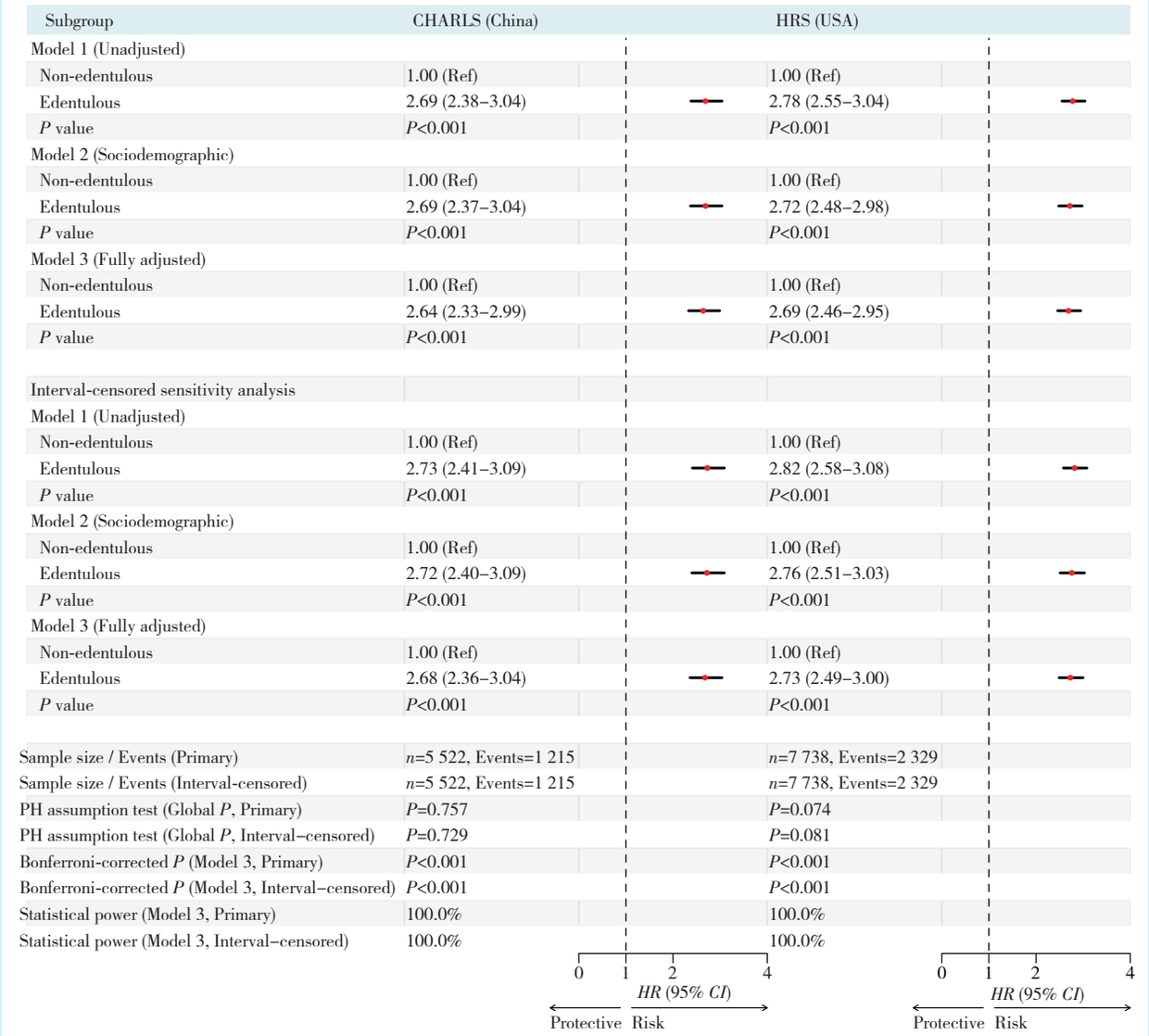
敏感性分析显示（图5），以心脏病、中风为单独结局、排除前2年事件、完整病例分析及Fine-Gray竞争风险模型的结果均与主分析（CHARLS：*HR* = 2.64；HRS：*HR* = 2.69）高度一致，未出现明显方向或效应量偏移。其中以中风为结局时效应最强（CHARLS：*HR* = 2.85；HRS：*HR* = 2.91）。

上述结果表明，全口缺牙与新发CVD的关联稳定可靠，不受反向因果、缺失数据及竞争事件的明显影响。

3　讨　论

本研究基于中国CHARLS与美国HRS两项大规模的纵向老年人群队列数据进行回顾性分析，通过长期随访设计，在东西方老年人群中同步证实基线全口缺牙状态与老年人新发CVD风险升高存在独立关联，且该关联在各亚组中保持一致，经多项敏感性分析验证稳健。为口腔健康与心血管疾病的因果关联提供了高质量、跨文化的流行病学证据。

本研究CHARLS队列中老年人全口缺牙患病率为16.2%，与第四次全国口腔健康流行病学调查报告的4.5%的全口无牙率存在明显差异，该差异由多重客观因素共同造成。首先两项研究纳入年龄范围不一致，第四次全国口腔流调仅限定65~74岁人群，而本研究纳入全部≥60岁老年人，包含75岁及以上高龄群体，且分层结果已证实全口缺牙患病率随年龄显著升高，因此高龄人群的纳入直接拉高整体患病率；其次口腔缺牙判定标准与检测方式存在区别，全国口腔流调由专业口腔医师开展现场临床检查，存在残根者不纳入全口无牙，而CHARLS采用问卷自报方式，佩戴全口义齿、口内仅存残根的受访者均可能自报为“全口缺牙”，可能导致全口缺牙比例偏高；最后是抽样设计与人群构成不同，第四次全国口腔流调覆盖全国31个省份，而CHARLS仅覆盖28个省份，且农村居民样本占比达64.2%。由于农村口腔医疗可及性不足，



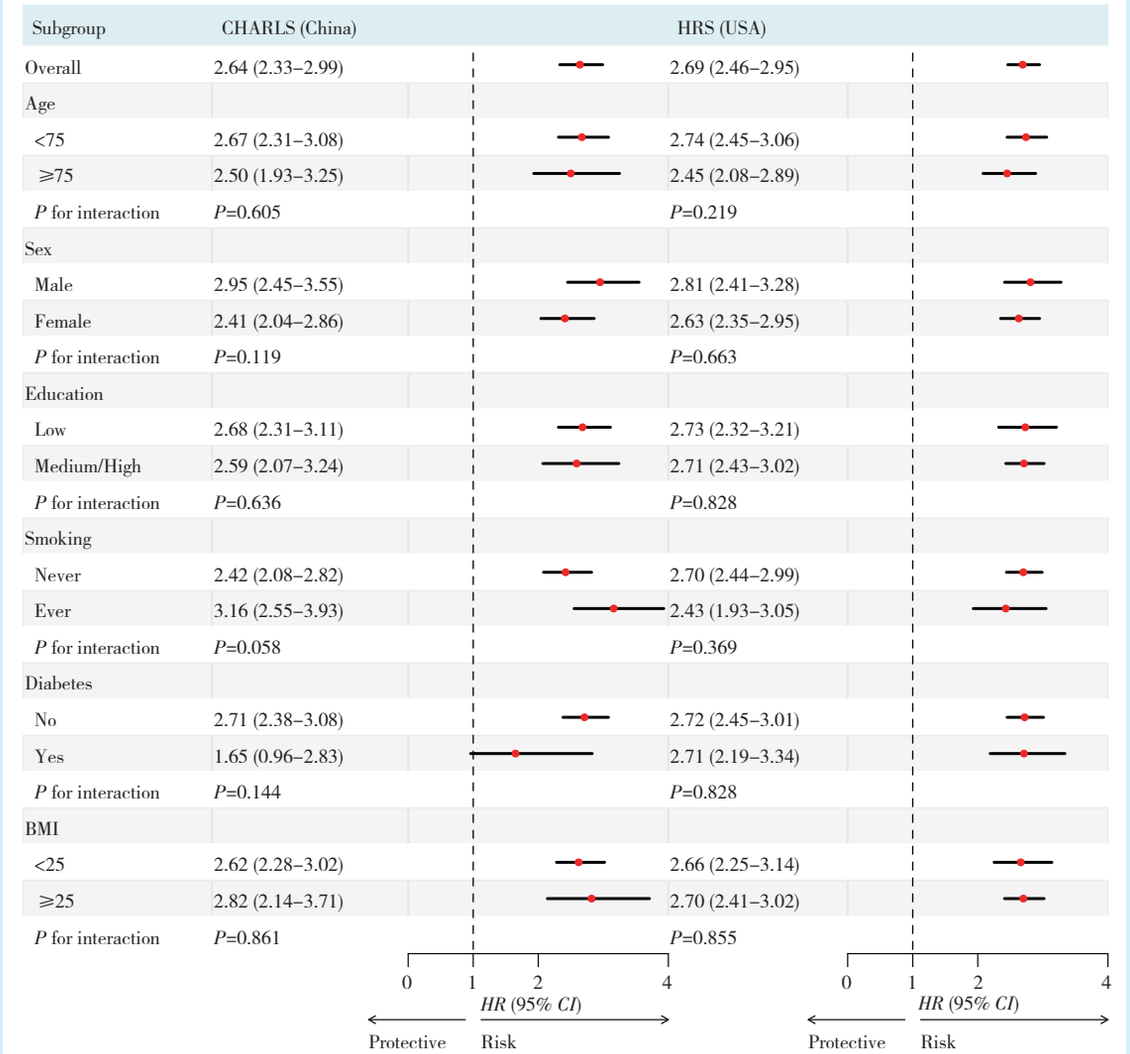
CHARLS: China Health and Retirement Longitudinal Study; HRS: Health and Retirement Study; CVD: cardiovascular disease

Figure 3　Forest plot of the association between complete edentulism and incident cardiovascular disease risk based on a Cox proportional hazards model and an interval-censored proportional hazards model

图3　全口缺牙与心血管疾病发生风险的Cox比例风险模型及区间删失模型分析森林图

全口缺牙人群占比更高。本研究16.2%的患病率与既往依托CHARLS数据库发表的国际研究结果相近[17]。上述提示人群筛选与变量提取流程可靠，患病率差异并非数据处理偏差导致。

从病理生理机制层面分析，全口缺牙作为牙周疾病迁延发展的终末结局，可经由多条生物学通路参与心血管稳态失衡进程[18-19]。首先，全口缺牙往往伴随长期重度牙炎、反复龋病及持续性口腔慢性感染，此类口腔病变会持续诱导机体处于低度系统性炎症状态，促使外周血中C反应蛋白、白细胞介素-6和纤维蛋白原等系统性炎症标志物持续高表达，长期损伤血管内皮完整性，加速血管壁脂质沉积与泡沫细胞形成，进而推进动脉粥样硬化和心脑血管事件的病理进程[20-23]。其次，长期炎症造成的牙周黏膜破损，可促使牙周致病菌及其DNA侵入血液循环引发菌血症，已有研究证实牙周病原体在动脉粥样硬化斑块中的检出率显著高于健康血管组织，提示其可直接定植于血管壁，诱导血小板异常活化与微小血栓形成，加剧血管硬化与管腔狭窄，最终升高CVD事件发病风



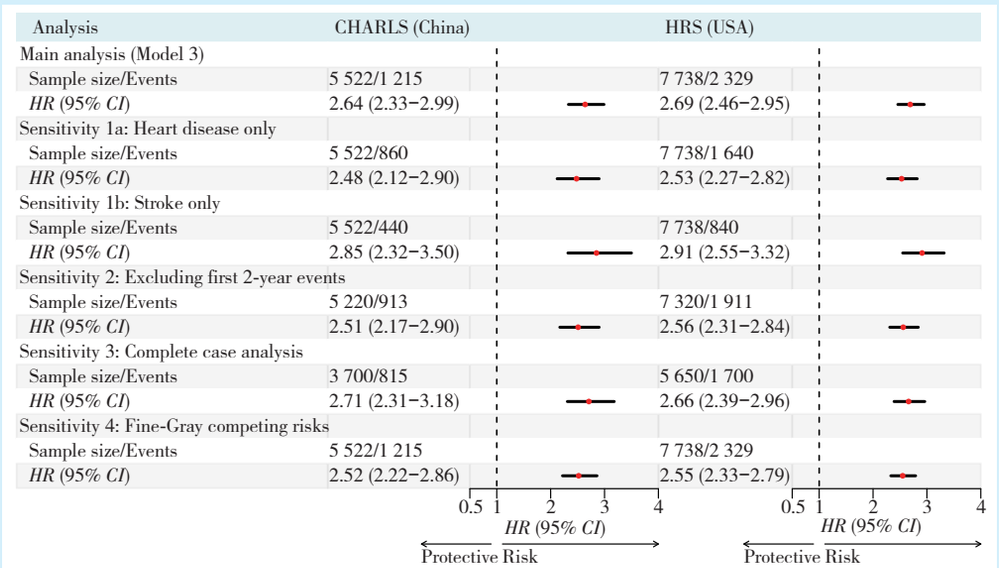
CHARLS: China Health and Retirement Longitudinal Study; HRS: Health and Retirement Study; CVD: cardiovascular disease; BMI: body mass index. The overall analytic sample comprised 5 522 participants from CHARLS and 7 738 from HRS. Interaction *P* values were calculated using likelihood ratio tests

Figure 4　Forest plot of a subgroup analysis for the association between complete edentulism and cardiovascular disease

图4　全口缺牙与心血管疾病发生风险的亚组分析森林图

险[24-27]。此外，全口缺牙会导致口腔咀嚼功能完全丧失，迫使老年人群饮食结构更偏向精细与高热量食物，进而引发体重、血糖及血脂异常，并与高血压、糖尿病等传统CVD危险因素形成协同致病效应，进一步放大心血管损伤风险[28-31]。以上提示全口缺牙可通过系统性炎症、致病菌侵袭、代谢紊乱三大途径影响心血管系统稳态。这为本研究观察到的全口缺牙与CVD的显著独立关联提供了充分的生物学解释，也印证了二者关联并非单纯统计学相关，而是具有坚实的病理生理基础。

本研究的创新之处在于：①不同于多数研究存在单一国家、小样本或横断面设计等局限性，本研究同步纳入中美两国老年人群队列，在调整多项混杂因素后，进一步证实全口缺牙与CVD的独立关联并非由地域或人群特征驱动，提示结果具备良好的外推性。②在关联效应幅度上，所观察到的全口缺牙与CVD的关联强度（CHARLS：*HR* = 2.64；HRS：*HR* = 2.69），高于既往多数Meta分析所报告的缺牙与CVD风险的合并效应估计[32-33]，这一效应差异与前述病理机制相呼应。③由于既往研究多采用连续性牙齿缺失计数、部分缺牙作为暴露指标，纳入了大量口腔损伤较轻、炎症负荷较



CHARLS: China Health and Retirement Longitudinal Study; HRS: Health and Retirement Study; CVD: cardiovascular disease. The primary analysis included 5 522 participants in CHARLS and 7 738 in HRS

Figure 5　Forest plot of a sensitivity analysis for the association between complete edentulism and cardiovascular disease risk

图5　全口缺牙与心血管疾病发生风险的敏感性分析森林图

低、咀嚼功能未完全丧失的人群，导致整体关联效应被稀释低估。而本研究精准聚焦全口缺牙这一口腔疾病终末状态，其病理严重程度高于普通缺牙人群，充分说明全口缺牙是老年人群CVD的强特异性危险因素。值得注意的是，全口缺牙与中风的关联强度高于其与心脏病事件的关联，与现有研究提示口腔感染对脑血管事件影响更显著的观点相吻合[34-36]。其潜在机制可能包括脑血管对系统性炎症及内皮损伤更为敏感，牙周致病菌可通过颈动脉途径更易定植于脑动脉血管壁[37-38]。该差异关联进一步从结局特异性角度增强了全口缺牙与CVD因果关联的生物学合理性与可信度。为补充相对风险指标的临床解读，本研究基于Kaplan-Meier分析提供各队列随访期内的绝对风险估计。CVD累积发病风险计算方法为：1−CVD无事件生存概率，在CHARLS队列，非全口缺牙组CVD累积发病风险约为21.78%（CVD无事件生存概率78.22%），全口缺牙组约为48.21%（CVD无事件生存概率51.79%），绝对风险差约26.4个百分点；在HRS队列，非全口缺牙组约为33.77%（CVD无事件生存概率66.23%），全口缺牙组约为72.21%（CVD无事件生存概率27.79%），绝对风险差约38.4个百分点。上述绝对风险为未经协变量调整的粗估计值，但直观地揭示了全口缺牙与CVD发病风险之间在临床层面的实质性差异。由于两个队列随访时长不同，且基线风险水平存在差异，故未统一转换为特定时间窗口（如10年）的绝对风险[39-40]（ClinicalTrials.gov：NCT05466825[40]）。主分析仍以调整后的*HR*作为主要效应估计指标，更适用于跨人群比较。

综上，本研究通过中美两大代表性老年人群队列一致证实，全口缺牙与新发CVD风险呈显著、独立且稳定的正向关联。这一发现为老年人群CVD的早期风险识别提供了低成本、易筛查、可推广的新型指标，同时，将全口缺牙评估纳入老年人群CVD常规风险筛查体系，可有效补充传统危险因素的评估局限，进一步提升老年人群心血管风险分层的精准度与覆盖范围。然而本研究仍存在一定局限性，首先体现在暴露（全口缺牙）与CVD事件结局（心脏病、中风）均基于受试者自报信息，可能存在一定程度的信息偏倚。另外，由于CHARLS和HRS采用周期性随访设计，CVD事件发生时间无法精确定位，仅能确定于两个随访波次之间。其次中美两国医疗保障、基层口腔服务、老年慢性病筛查体系、居民健康认知存在显著差异，可能带来跨队列测量异质性偏倚。此外，缺牙数量与CVD风险的剂量－反应关系未进行分层讨论。未来可开展标准化口腔临床查体、调取医院

电子病历客观记录暴露与结局，针对中、美等不同医疗体系人群开展测量偏差校准分析，并采用包含详细缺牙颗数信息的数据库进一步验证剂量－反应关系。精准解析缺牙与CVD之间的因果链条，为推动口腔健康融入CVD综合防控，降低全球老年人群CVD疾病负担提供更充分的循证依据。

【Author contributions】 Jia L analyzed the data and wrote the article. Ren BJ participated in data interpretation and reviewed the article. He YL designed the study and revised the article. All authors read and approved the final manuscript as submitted.

【Ethics statement】 This study was conducted in accordance with the principles of the Declaration of Helsinki. The CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11015), and the HRS study was approved by the Institutional Review Board of the University of Michigan (HUM00061128). This secondary analysis of de-identified publicly available data did not require additional ethical approval.

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【Competing interests】 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: all authors declare that there are no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

【Data availability statement】 The datasets used in this study are publicly available from the China Health and Retirement Longitudinal Study (CHARLS, http://charls.pku.edu.cn/) and the Health and Retirement Study (HRS, https://hrs.isr.umich.edu/). The data are available to qualified researchers upon reasonable application through the respective database platforms.

【Generative AI statement】 The authors declared that generative AI was not used in the creation of this manuscript.

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