

血清维生素 D 水平与心肾代谢疾病进展风险的关联:来自英国生物银行前瞻性队列的证据

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【摘要】 目的 评估基线血清维生素 D 水平与心肾代谢疾病(cardio-renal-metabolic disease, CRMD)发生、进展及死亡的关联,并探讨人群特征的修饰作用。方法 基于英国生物银行 377 861 名基线无 CRMD 参与者的前瞻性队列,利用 Cox 模型和多状态模型(multi-state model, MSM)分析血清维生素 D 水平与首次 CRMD(first CRMD, FCRMD)、心肾代谢共病(cardio-renal-metabolic multimorbidity, CRMM)及死亡风险的关联,并进行限制性立方样条及分层分析。结果 共观察到 64 804 例 FCRMD 事件和 15 725 例 CRMM 事件。Cox 模型显示,血清维生素 D 不足和缺乏均显著增加 FCRMD、CRMM 及死亡风险,血清维生素 D 缺乏组的 CRMM 风险升高最明显(HR=1.29, 95%CI:1.24~1.35)。MSM 显示,血清维生素 D 缺乏使 FCRMD 向 CRMM 进展的风险增加 13%,CRMD 死亡风险增加 21%以上,并在心血管疾病与 2 型糖尿病路径中关联最显著。血清维生素 D 浓度与 CRMD 风险呈 U 型关联,最低点约为 50 nmol/L。分层分析提示肥胖人群和低社会经济地位人群 CRMD 发生及进展风险上升更显著。结论 低血清维生素 D 水平与 CRMD 发生及进展风险增加存在显著关联,且在肥胖及低社会经济地位人群中的关联更为明显。维持适宜的血清维生素 D 水平可能有助于预防 CRMD 发生及进展。

【关键词】 心肾代谢疾病(CRMD); 心肾代谢共病(CRMM); 维生素 D; 多状态模型(MSM)

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Association between serum vitamin D level and risk of cardio-renal-metabolic disease progression: evidence from a large prospective UK Biobank cohort

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【Abstract】 **Objective** To evaluate the association between baseline serum vitamin D levels and the occurrence, progression, and mortality risk of cardio-renal-metabolic disease (CRMD), and to explore the modifying effect of population characteristics. **Methods** Based on a prospective cohort study of 377 861 participants free of CRMD at baseline from the UK Biobank, the Cox model and a multi-state model (MSM) were used to analyze the associations between serum vitamin D levels and the risk of first CRMD (FCRMD), cardio-renal-metabolic multimorbidity (CRMM), and death. In addition, restricted cubic spline and stratified analyses were conducted. **Results** A total of 64 804 FCRMD events and 15 725 CRMM events were observed. The Cox model showed that both insufficient and deficient serum vitamin D levels significantly increased the risk of FCRMD, CRMM, and death. The risk of CRMM was the highest

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in the serum vitamin D deficiency group (HR=1.29, 95%CI: 1.24–1.35). The MSM indicated that deficient serum vitamin D level increased the risk of progression from FCRMD to CRMM by 13% and the risk of death after CRMD by more than 21%, and its association was most significant on cardiovascular disease and type 2 diabetes pathways. Serum vitamin D concentration was associated with CRMD risk in a U-shaped pattern, with the lowest point approximately at 50 nmol/L. Stratified analysis indicated that the risk of occurrence and progression of CRMD was significantly higher in obese individuals and those with low socioeconomic status. **Conclusion** Low serum vitamin D levels were significantly associated with an increased risk of CRMD occurrence and progression, and the association was more pronounced in obese and low socioeconomic status populations. Maintaining an appropriate serum vitamin D level may help prevent the occurrence and progression of CRMD.

【Key words】 cardio-renal-metabolic disease (CRMD); cardio-renal-metabolic multimorbidity (CRMM); vitamin D; multi-state model (MSM)

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心血管疾病(cardiovascular disease, CVD)、2型糖尿病(type 2 diabetes, T2D)和慢性肾脏病(chronic kidney disease, CKD)是21世纪的主要公共卫生问题。Marassi等^[1]首次提出心肾代谢疾病(cardio-renal-metabolic disease, CRMD)的概念,强调三者之间存在密切的病理生理学联系。个体在首次CRMD(first CRMD, FCRMD)后可能会进展为心肾代谢共病(cardio-renal-metabolic multimorbidity, CRMM),即2或3种CRMD共存,显著增加多器官功能障碍和不良心血管结局风险^[1-2]。一项包含68万名参与者的研究发现,T2D、心肌梗死及卒中等均显著增加全因死亡风险,而当这些疾病共存时,死亡风险呈倍增效应,且风险水平因不同的疾病组合而异^[3],提示CRMD进展路径上可能存在疾病特异性。

血清维生素通常指25-羟基维生素D[25-OH vitamin D, 25(OH)D],其参与多种生理过程,包括钙代谢、免疫调节及血管内皮功能调控等^[4-6]。大量观察性研究发现较低的维生素D水平与CRMD风险升高相关,但随机对照试验结果尚不一致,提示其作用可能存在阈值效应,并受个体特征影响^[7]。既往研究多聚焦于单一疾病或结局,缺乏对共病进展的证据,且常受样本量及竞争风险的限制,社会人口学因素的效应修饰作用亦未明确。

本研究基于英国生物银行前瞻性队列,采用多状态模型(multi-state model, MSM)探讨维生素D水平与CRMD的发生、进展及死亡风险的关联,并评估潜在效应修饰。

资料和方法

研究对象 英国生物银行是一项基于人群的前瞻性队列研究,该研究于2006年至2010年期间从约50万名年龄在40~69岁的居民中招募参与者。所有参与者都签署了知情同意书,且该研究已获得国家医疗服务体系国家研究伦理服务的批准(批准号:11/NW/0382)。本研究基于UK Biobank数据开展,数据使用申请编号为98410。排除基线前确证的CVD、T2D或CKD的参与者、缺少25(OH)D数据和其他协变量的参与者后,最终研究纳入377 861名参与者。

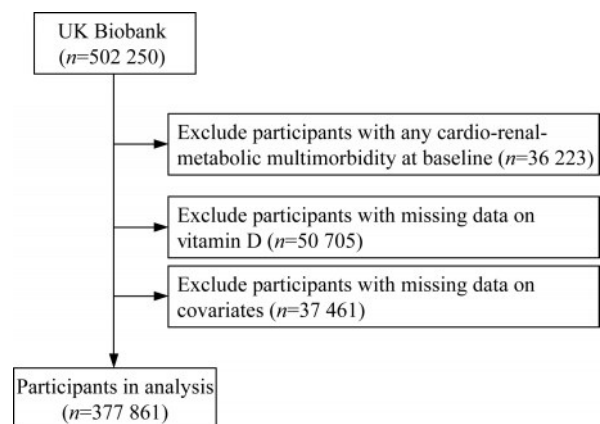


图1 研究参与者的流程图

Fig 1 Flowchart of study participants

暴露定义 为评估血清维生素D严重缺乏人群与边缘不足人群的风险差异,本研究采用美国医学研究所推荐的血清25(OH)D分组标准,将

25(OH)D水平划分为缺乏(<30 nmol/L)、不足($30\sim50$ nmol/L)和充足(≥ 50 nmol/L)。血清25(OH)D浓度采用DiaSorin Ltd.公司的LIAISON XL化学发光免疫分析系统测定^[8]。该检测通过RIQAS免疫测定专业I质量评价方案进行外部质量控制,质量保证合格率为100%^[8]。

结局与随访时间定义 参考既往研究,CRMD包括CVD、T2D和CKD,FCRMD定义为随访期间首次发生CVD、T2D和CKD中任一疾病。CRMM定义为FCRMD后,个体再新增至少一种不同类别的CRMD^[2]。CVD(I11, I20~I25, I42, I48~I50, I70, I73)、T2D(E11, E14)和CKD(N18)的诊断是根据国际疾病分类第10版(ICD-10)来确定的^[9-11]。从基线至首次发生结局事件、失访、死亡或随访截止日期的时间定义为随访时间。

协变量定义 将多个人口学、生活方式因素作为协变量纳入分析。人口学变量包括年龄(≥ 60 岁为高龄)、性别(男性/女性)、种族(白种人/其他)、教育水平(无学历、其他学历、大学及以上学历)及以Townsend剥夺指数[按中位数分为高社会经济地位(socioeconomic status, SES)和低SES]。生活方式因素包括吸烟状态(从不、既往、当前),饮酒状态(从不、既往、当前),BMI(<18.5 、 ≥ 18.5 且 <25.0 、 ≥ 25.0 且 <30.0 、 ≥ 30.0 ,单位:kg/m²),体力活动水平^[2](达到WHO的推荐标准/未达到推荐标准),饮食模式^[2](按照美国饮食指南评估分为健康饮食模式/不健康饮食模式),高血压史^[12](是/否)、夏季与冬季户外活动时间(<1 h、 $1\sim 2$ h、 $3\sim 4$ h、 ≥ 5 h)以及防晒/紫外线防护使用频率(从不或很少 vs. 经常或总是)。

统计学分析 统计分析均在R软件(版本4.4.1)中完成。研究对象特征中连续变量以 $\bar{x}\pm s$ 报告,分类变量以 $n(\%)$ 报告。为评估基线血清维生素D水平与FCRMD、CRMM和死亡的关联,首先构建了Cox比例风险模型。模型1仅调整年龄、性别、种族,模型2在模型1的基础上进一步对教育水平、Townsend剥夺指数、BMI、吸烟及饮酒状态、体力活动水平、饮食模式、户外活动时间、防晒使用等协变量进行调整。在此基础上,采用限制性立方样条检验血清维生素D浓度与结局之间的潜在非线性剂量-反应关系。为进一步探讨血清维生素D水平对CRMD纵向进展过程的影响,我们构建了MSM,基于基线 $\rightarrow$ FCRMD $\rightarrow$ CRMM $\rightarrow$ 死亡的转

移过程,构建5条状态转移路径,分析不同血清维生素D水平人群各状态转移风险。对同日发生多个状态事件的参与者,将前一状态进入日期设为后一状态进入日期减0.5天^[2, 12]。此外,为进一步探讨不同疾病类型的进展差异,我们构建了由CVD、T2D、CKD、CVD+T2D、CVD+CKD、T2D+CKD、CVD+T2D+CKD组成的疾病特异性模型,即考虑了7种状态之间的12条转移路径。由于多状态模型需明确不同疾病的发生顺序,强行调整时间可能导致路径错分,故排除在同一天诊断了不同疾病的参与者($n=4\,794$),最终373\,067名参与者纳入疾病特异性分析。针对部分协变量存在缺失的情况,本研究采用多重插补法生成5个插补数据集,并在插补数据集中重复上述多状态模型分析,汇总结果作为敏感性分析。此外,研究人群按年龄、性别、社会经济地位SES及BMI等进行分层分析,并通过似然比检验评估交互作用。所有检验均为双侧检验,以 $P<0.05$ 为差异有统计学意义。

结 果

一般情况 在377\,861名参与者中,平均年龄为(56.0 ± 8.1)岁,45.6%参与者为男性,92.8%为白人。平均随访时间为13.4年,共观察到64\,804例FCRMD事件、15\,725例CRMM事件。与未发生CRMD的参与者相比,FCRMD组和CRMM组参与者年龄更大,男性比例更高,教育水平较低,Townsend剥夺指数较高,BMI较高,未达到推荐体力活动水平、不健康饮食、既往或当前吸烟与饮酒行为的比例更高,每日户外停留时长更长且较少或从不使用防晒霜的比例更高,有高血压病史的比例更高(表1)。

基线血清维生素D水平与结局之间的关系 表2展示了基线血清维生素D水平和各结局风险的关联。Cox模型结果显示,血清维生素D不足和缺乏均与FCRMD、CRMM及死亡风险显著相关。与血清维生素D充足组相比,血清维生素D不足组的FCRMD发生风险增加4%(HR=1.04, 95%CI: 1.03~1.06),血清维生素D缺乏组的FCRMD发生风险增加13%(HR=1.13, 95%CI: 1.11~1.16);两组CRMM发生风险则分别增加11%(HR=1.11, 95%CI: 1.07~1.15)和29%(HR=1.29, 95%CI: 1.24~1.35)。疾病特异性分析发现,血清维生素D缺乏与

表1 按疾病状态划分的参与者的基线特征

Tab 1 Baseline characteristics of study participants by incident disease states

[n(%) or $\bar{x} \pm s$]

Characteristic	No CRMD (n=297 332)	FCRMD (n=64 804)	CRMM (n=15 725)
Age (y)	54.95 $\pm$ 8.1	59.67 $\pm$ 7.1	61.58 $\pm$ 6.4
Sex			
Female	170 858 (57.5)	28 454 (43.9)	6 192 (39.4)
Male	126 474 (42.5)	36 350 (56.1)	9 533 (60.6)
Race			
Others	21 123 (7.1)	4 735 (7.3)	1 452 (9.2)
White	276 209 (92.9)	60 069 (92.7)	14 273 (90.8)
Education			
No qualification	37 614 (12.7)	14 275 (22.0)	4 786 (30.4)
Any other qualifications	150 531 (50.6)	32 322 (49.9)	7 523 (47.8)
College or university degree	109 187 (36.7)	18 207 (28.1)	3 416 (21.7)
Townsend deprivation index	-1.52 $\pm$ 2.95	-1.29 $\pm$ 3.10	-0.84 $\pm$ 3.29
BMI			
<18.5	1 678 (0.6)	262 (0.4)	33 (0.2)
[18.5-25.0)	111 297 (37.4)	16 115 (24.9)	2 169 (13.8)
[25.0-30.0)	12 6721 (42.6)	28 314 (43.7)	6 155 (39.1)
$\geq$ 30.0	57 636 (19.4)	20 113 (31.0)	7 368 (46.9)
Physical activity			
Inadequate	59 509 (20.0)	15 081 (23.3)	4 455 (28.3)
Enough	237 823 (80.0)	49 723 (76.7)	11 270 (71.7)
Dietary pattern			
Unhealthy	287 249 (96.6)	62 771 (96.9)	15 270 (97.1)
Healthy	10 083 (3.4)	2 033 (3.1)	455 (2.9)
Alcohol intake status			
Never	10 298 (3.5)	2 788 (4.3)	983 (6.3)
Previous	8 443 (2.8)	2 635 (4.1)	883 (5.6)
Current	278 591 (93.7)	59 381 (91.6)	13 859 (88.1)
Smoking status			
Never	172 401 (58.0)	31 759 (49.0)	6 668 (42.4)
Previous	96 607 (32.5)	25 157 (38.8)	6 864 (43.7)
Current	28 324 (9.5)	7 888 (12.2)	2 193 (13.9)
Hypertension history			
No	232 979 (78.4)	38 144 (58.9)	6 299 (40.1)
Yes	64 353 (21.6)	26 660 (41.1)	9 426 (59.9)
Time spent outdoors in summer (h/day)	3.66 $\pm$ 2.34	4.09 $\pm$ 2.47	4.30 $\pm$ 2.56
Time spent outdoors in winter (h/day)	1.87 $\pm$ 1.75	2.16 $\pm$ 1.92	2.29 $\pm$ 2.03
Sun screen use			
Never/less frequent	88 277 (29.7)	20 724 (32.0)	5 390 (34.3)
Most of times/always	209 055 (70.3)	44 080 (68.0)	10 335 (65.7)
Baseline vitamin D status			
Sufficient	137 450 (46.2)	29 173 (45.0)	6 334 (40.3)
Insufficient	101 956 (34.3)	22 180 (34.2)	5 541 (35.2)
Deficient	57 926 (19.5)	13 451 (20.8)	3 850 (24.5)

T2D发生风险的关联最为显著(HR=1.47,95%CI:1.43~1.52),未发现与CKD发生风险有统计学关联。限制性立方样条结果(图2)显示血清维生素D浓度与CRMD发生风险呈非线性的U型关联($P_{\text{非线性}} < 0.001$),最低风险对应的血清25(OH)D浓度约为50 nmol/L。

表2 基线血清维生素D与首次心肾代谢疾病、心肾代谢共病和死亡风险关联的Cox模型分析

Associations of baseline serum vitamin D and the risks of first cardio-renal-metabolic disease, cardio-renal-metabolic multimorbidity and death using the Cox model						
Baseline vitamin D	Insufficiency vs. Sufficiency			Deficiency vs. Sufficiency		
	Case ^a	Model 1 ^b	Model 2 ^c	Case ^a	Model 1 ^b	Model 2 ^c
FCRMD	27 721 (20.36)	1.12 (1.10, 1.14)	1.04 (1.03, 1.06)	17 301 (22.47)	1.32 (1.29, 1.34)	1.13 (1.11, 1.16)
CRMM	5 541 (3.71)	1.27 (1.23, 1.32)	1.11 (1.07, 1.15)	3 850 (4.52)	1.70 (1.63, 1.77)	1.29 (1.24, 1.35)
Death	9 068 (5.98)	1.14 (1.10, 1.17)	1.09 (1.06, 1.12)	6 436 (7.42)	1.57 (1.52, 1.62)	1.37 (1.33, 1.41)
CVD	20 511 (14.58)	1.06 (1.04, 1.08)	1.01 (1.00, 1.03)	12 218 (15.22)	1.21 (1.18, 1.23)	1.08 (1.06, 1.11)
T2D	8 768 (5.99)	1.46 (1.42, 1.51)	1.23 (1.19, 1.27)	6 775 (8.19)	2.02 (1.95, 2.08)	1.47 (1.43, 1.52)
CKD	4 715 (3.15)	1.04 (1.00, 1.08)	0.95 (0.91, 0.98)	2 733 (3.19)	1.18 (1.12, 1.23)	0.98 (0.93, 1.02)

^aRate per 1 000 person-years; ^bAdjusted for age, sex, race; ^cFurther adjusted for education, Townsend deprivation index, BMI, smoking status, drinking status, time spent outdoors in summer or winter, sun screen/UV protection use.

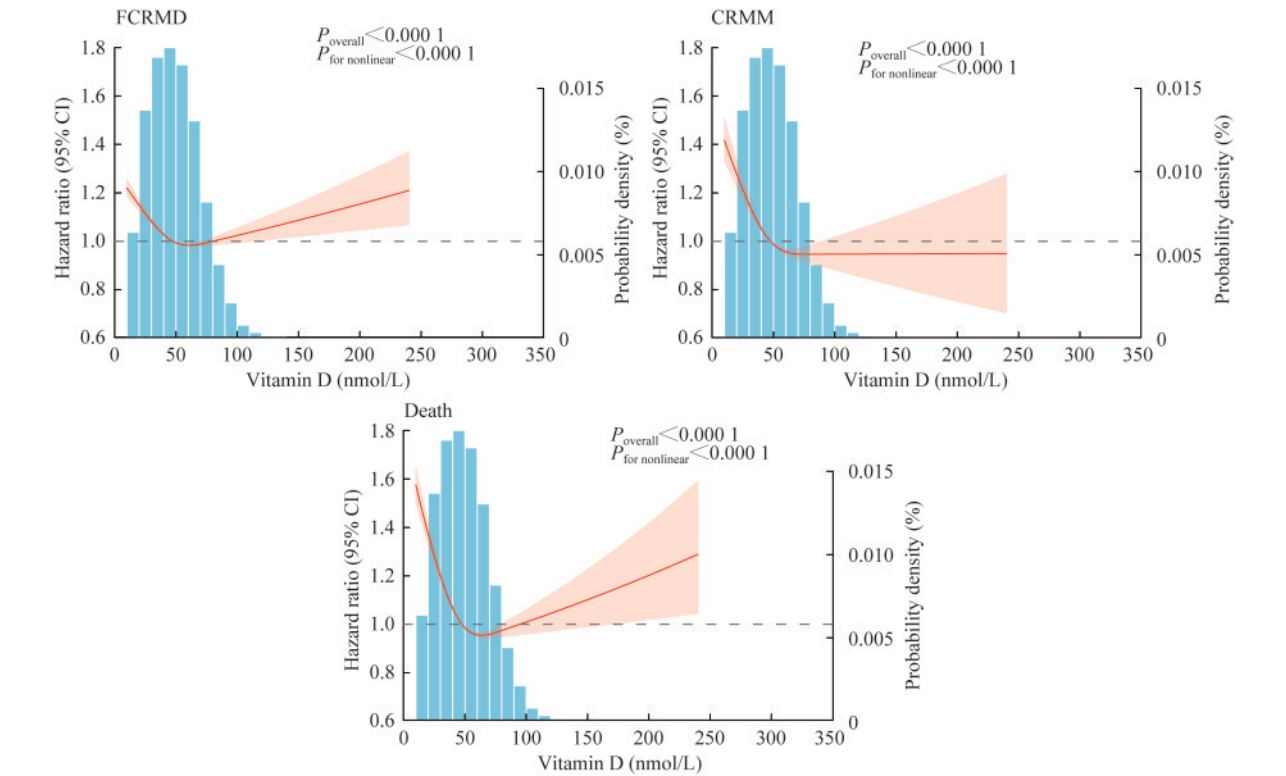
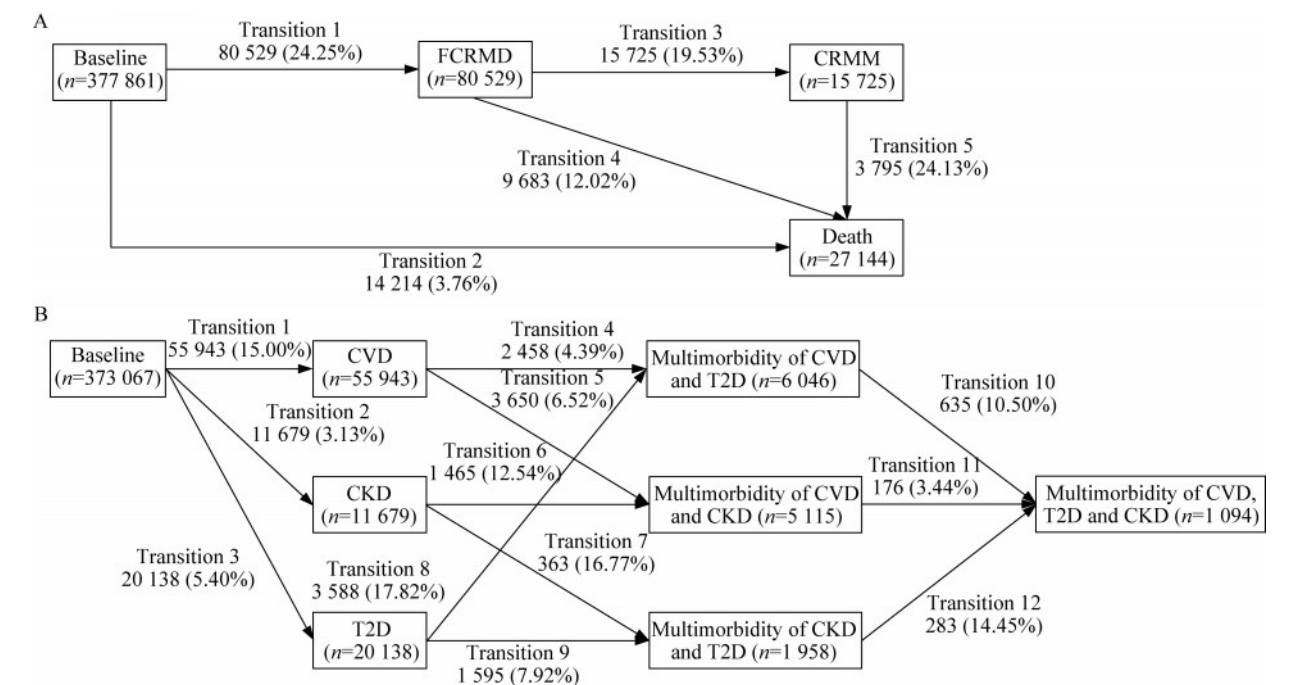


图2 限制性立方样条分析基线血清维生素D和CRMD的剂量反应关联

Fig 2 Dose-response relationship of baseline serum vitamin D concentration and CRMD risk analyzed by restricted cubic spline analysis

血清维生素D水平对CRMD纵向进展的影响 CRMD纵向进展过程中各状态参与者数量及百分比如图3所示。在转移模式A中,24.25%的参与者发生了FCRMD;19.53%的FCRMD患者进一步进展为CRMM;24.13%的CRMM参与者死亡(图3A)。在疾病特异性的转移模式B中,55 943例(15.00%)是CVD首发病例、11 679例(3.13%)是CKD首发病例,

20 138例(5.40%)是T2D首发病例(图3B)。多状态模型结果(表3)显示,与基线血清维生素D较充足者相比,不足者的FCRMD发生风险和CRMM发生风险分别升高4%(HR=1.04,95%CI:1.02~1.05)和6%(HR=1.06,95%CI:1.02~1.10),缺乏者则分别升高13%(HR:1.13,95%CI:1.11~1.15)和15%(HR=1.15,95%CI:1.10~1.20)。基线



A: Transition pattern from baseline to FCRMD, CRMM and death; B: Transition pattern from baseline to specific FCRMD, then to specific two CRMM, and ultimately to three CRMM.

图3 CRMD纵向进展过程中参与者数量及百分比

Fig 3 Numbers and percentages of participants in longitudinal CRMD progression

血清维生素D缺乏还显著增加FCRMD至死亡(HR=1.21, 95%CI: 1.14~1.27)及CRMM至死亡(HR=1.24, 95%CI: 1.13~1.36)的风险。多重插补后的结果与主分析结果一致。疾病特异性分析提示,其在CVD与T2D共病进展路径中的关联最强。CVD→CVD+T2D: HR(95%CI)=1.24(1.11~1.38); T2D→T2D+CVD: HR(95%CI)=1.15(1.05~1.25)。

表3 评估基线血清维生素D水平与不同过渡关联的多状态模型

Tab 3 Multistate model assessing associations between baseline serum vitamin D levels and different transitions

[HR (95%CI)]

Transition	Baseline vitamin D levels (ref: sufficiency)	
	Insufficiency	Deficiency
Transition pattern A		
Baseline→FCRMD	1.04 (1.02, 1.05)	1.13 (1.11, 1.15)
Baseline→Death	1.09 (1.05, 1.14)	1.36 (1.30, 1.42)
FCRMD→CRMM	1.06 (1.02, 1.10)	1.15 (1.10, 1.20)
FCRMD→Death	1.04 (0.99, 1.09)	1.21 (1.14, 1.27)
CRMM→Death	0.98 (0.90, 1.07)	1.24 (1.13, 1.36)
Transition pattern B		
Baseline→CVD	1.00 (0.98, 1.02)	1.04 (1.01, 1.06)
Baseline→T2D	1.24 (1.19, 1.28)	1.48 (1.42, 1.54)

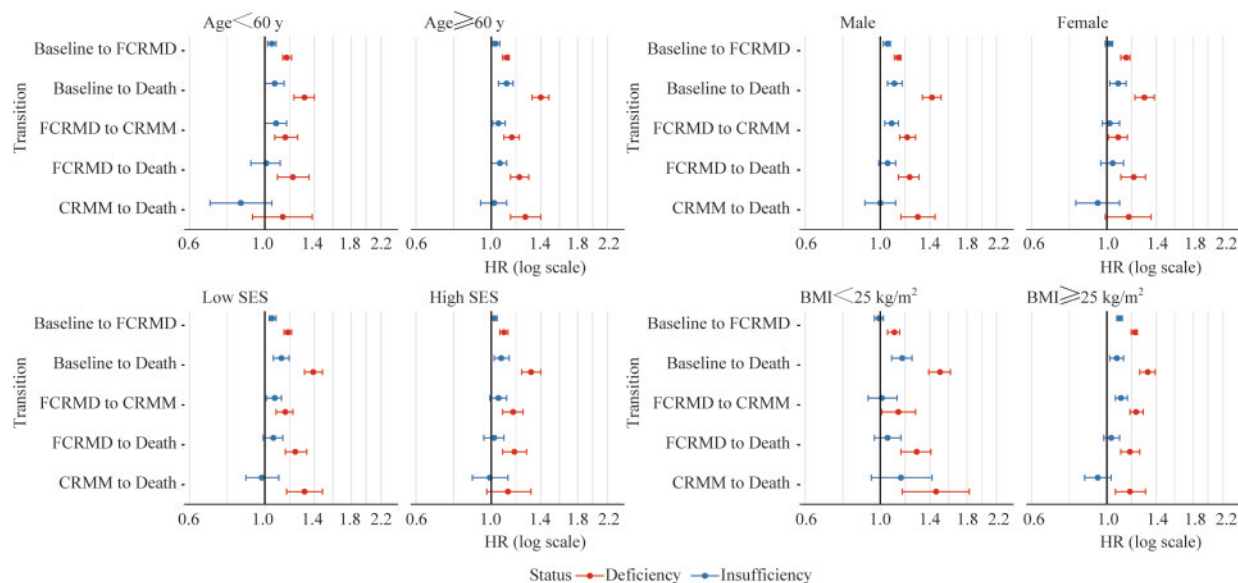
(续表3)

Transition	Baseline vitamin D levels (ref: sufficiency)	
	Insufficiency	Deficiency
Baseline→CKD	0.88 (0.83, 0.93)	0.85 (0.79, 0.91)
CVD→CVD+T2D	1.14 (1.04, 1.26)	1.24 (1.11, 1.38)
CVD→CVD+CKD	0.96 (0.88, 1.04)	0.96 (0.86, 1.06)
T2D→T2D+CVD	1.04 (0.96, 1.13)	1.15 (1.05, 1.25)
T2D→T2D+CKD	0.90 (0.78, 1.05)	0.83 (0.70, 0.99)
CKD→CKD+CVD	1.01 (0.89, 1.15)	1.11 (0.94, 1.31)
CKD→CKD+T2D	1.16 (0.83, 1.63)	1.27 (0.85, 1.88)
CVD+T2D→CVD+T2D+CKD	0.94 (0.88, 1.01)	0.92 (0.84, 1.00)
CVD+CKD→CVD+T2D+CKD	1.10 (1.02, 1.19)	1.24 (1.13, 1.35)
CKD+T2D→CVD+T2D+CKD	0.93 (0.83, 1.05)	0.91 (0.79, 1.06)
Transition pattern A after 5 times of multiple imputation (n=415 322)		
Baseline→FCRMD	1.04 (1.02, 1.05)	1.14 (1.12, 1.16)
Baseline→Death	1.10 (1.06, 1.14)	1.36 (1.30, 1.42)
FCRMD→CRMM	1.05 (1.01, 1.08)	1.15 (1.10, 1.20)
FCRMD→Death	1.07 (1.02, 1.12)	1.22 (1.16, 1.28)
CRMM→Death	0.99 (0.91, 1.07)	1.17 (1.08, 1.28)

Adjusted for age, sex, race, education, Townsend deprivation index, BMI, hypertension history, smoking status, drinking status, physical activity, dietary pattern, time spent outdoors in summer or winter, Sun screen/UV protection use.

图4展示了基线血清维生素D水平与CRMD不同转移风险关联的分层分析结果。年龄分层结果显示,年轻人低基线血清维生素D水平与FCRMD发生风险增加的关联更为明显,老年人中基线血清维生素D缺乏与CRMM至死亡风险增加的关联更强(HR=1.26, 95%CI: 1.14~1.40)。性别分层结果显示,女性仅在基线血清维生素D缺乏时

FCRMD发生风险显著增加(HR=1.14, 95%CI: 1.10~1.17)。SES分层结果表明,低SES人群中低基线血清维生素D与CRMD发生及进展风险增加的关联更明显。此外,在超重/肥胖人群中,无论血清维生素D不足还是缺乏,均与FCRMD风险增加显著相关(HR分别为1.09和1.21),类似结果亦见于FCRMD至CRMM转移路径。



SES was classified according to the Townsend deprivation index; values $\geq$ the median were defined as low SES, and values $<$ the median as high SES.

图4 基线血清维生素D水平与不同状态转移风险关联的分层分析结果

Fig 4 Stratified analyses of the associations between baseline serum vitamin D levels and different state transitions

讨论

本研究基于英国生物银行队列,系统评估了基线血清维生素D水平与CRMD纵向进展的关联。结果显示,基线血清维生素D水平较低与FCRMD、CRMM及死亡风险增加显著相关,剂量反应关系呈U型曲线,最低风险对应的25(OH)D浓度约为50 nmol/L。上述关联在肥胖及低社会经济地位人群中更为明显($P_{交互} < 0.05$)。

已有大量研究证实维生素D与多种常见慢性疾病相关,但针对这些存在显著相互作用的疾病群,维生素D的作用尚无系统评估。3篇Meta分析均报告较低维生素D水平与CVD发病和死亡风险增高存在显著关联^[13-15]。此外,一项纳入多项大型随机对照试验的Meta分析显示,糖尿病高危人群补充维生素D 2年,可使其发生T2D的风险降低约

15%^[16]。本研究结果与既往文献基本一致。其可能的生物学机制包括维生素D受体(vitamin D receptor, VDR)广泛表达于多种组织,1,25-(OH)₂D与VDR结合后可作为转录因子调控炎症和代谢相关基因表达^[17-18]。此外,VDR缺失模型显示其可导致胰岛素抵抗及肾素-血管紧张素系统活化,诱发高血压和心肌肥厚^[19]。维生素D还可通过调节钙稳态、免疫反应参与心血管及代谢性疾病的进程^[4-5, 20]。但是本研究未在CKD的路径上观察到显著关联。有研究发现在非糖尿病人群中,血清25(OH)D与新发CKD之间并无显著关联^[21],提示维生素D与CKD的关联可能受血糖等因素调节,表现出不同的关联趋势。此外,本研究发现基线血清维生素D水平与CRMD发生风险之间存在显著的U型剂量-反应关系。已有部分CVD、T2D及全因死亡的前瞻性研究报告非线性趋势^[22-24]。不同研究观察到的剂量-反应曲线形态存在差异。基于糖尿病及糖前期

人群的2项研究中发现维生素D与CVD风险呈L型曲线^[22-23],这提示维生素D的作用可能随不同疾病背景、潜在混杂因素而表现出不同的关联模式^[25-26]。此外,研究观察到的风险最低水平与美国医学研究所提出的50 nmol/L一致^[27],提示维持适宜的血清维生素D水平可能有助于预防CRMD的发生与进展。

较低的血清维生素D水平不仅与首次CRMD发生风险增加相关,还与CRMM发生及死亡转移风险增加相关,其中CVD与T2D共病转移路径的关联最强,提示维生素D在心脏代谢性疾病的作用可能更为关键。本研究结果与某前瞻性研究相呼应,该研究发现糖尿病及糖前期人群中低维生素D水平与CVD及全因死亡显著相关^[22]。分层结果显示低维生素D水平的不良作用在肥胖及低社会经济地位人群中更为显著,与既往研究中报道一致^[19,28-29],提示个体特征的潜在修饰效应。本研究从CRMM纵向进展的视角补充了现有证据,为理解维生素D在CRMD网络中的进展路径及高危人群识别提供了新的证据支持。

本研究亦存在一定局限性:血清维生素D浓度为基线测量数据,无法反映随访期间维生素D的动态变化;虽然调整了多种混杂因素,但研究中所有协变量均基于基线测量,未能捕捉其时变特征,残余混杂难以完全排除;研究人群主要为英国白种人(92.8%),不同种族人群在维生素D代谢特征、CRMD发病风险及遗传背景上可能存在显著差异^[30]。因此,本研究结论在其他种族或不同国家、地区人群中的适用性有限,需谨慎外推。

综上,本研究发现较低维生素D水平与CRMD的发生及进展风险显著增加,尤其在心血管和糖尿病路径上作用最为突出,并呈U型剂量-反应关系;这一关联在肥胖及低社会经济地位人群中更为明显。未来仍需在不同人群中开展研究,结合维生素D动态变化进一步验证本研究结果,并探讨其潜在生物学机制及在高危人群精准防治中的应用价值。

作者贡献声明 蒋梓轩 研究构思,数据整理和分析,论文撰写和修订。秦国友 研究构思和指导。

利益冲突声明 所有作者均声明不存在利益冲突。

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