论著·公共卫生智库

残余胆固醇炎症指数的变异性与卒中风险存在剂量反应关系:来自中国开滦队列的证据

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[**摘要**] **目的** 探究新兴的综合生物标志物残余胆固醇炎症指数(remnant cholesterol inflammatory index,RCII)的变异性与卒中发生风险的关联,为卒中的预防提供更多理论基础。**方法** 应用前瞻性队列研究,选取连续参加2006年度、2008年度、2010年度体检的开滦研究人群(n=38 659)作为研究对象,以RCII的变异性四分位进行分组,RCII的变异性用标准差(standard deviation,SD)和平均真实变异性(average real variability,ARV)表示,每2年进行1次随访,以发生卒中(包括缺血性卒中、出血性卒中)、死亡或随访结束(2022年12月31日)为随访终点,采用Kaplan-Meier法计算不同分组发生终点事件的累积发病率,并用Log-Rank检验比较各组终点事件累积发生率的差异;采用多因素Cox比例风险回归模型分析RCII的变异性与卒中发生风险的关联。**结果** 38 659名观察对象在平均随访(11.22±2.26)年后,发生卒中者共2 539名。校正混杂因素后,以RCII-SD四分位分组,与Q1组相比,Q2组-Q4组发生卒中的*HR*分别为1.034(95%*CI*:0.917~1.167,P=0.584)、1.146(95%*CI*:1.018~1.290,P=0.025)、1.209(95%*CI*:1.066~1.370,P=0.003),P_{trend}<0.05;以RCII-ARV四分位分组,与Q1组相比,Q2组-Q4组发生卒中的*HR*分别为1.008(95%*CI*:0.894~1.136,P=0.901)、1.109(95% *CI*:0.986~1.248,P=0.085)、1.152(95%*CI*:1.018~1.303,P=0.025),P_{trend}<0.05。此外,敏感性分析及分层分析均得出类似结论。**结论** RCII的变异性与卒中有显著相关性,随着RCII的变异性的增加,卒中的发生风险也随之增加。**对策** 有关部门可以以降低RCII变异性为核心,建立定期监测机制,强化生活方式干预,规范饮食、运动及体重管理,抑制指数波动。用药坚持平稳降脂原则,优选疗效稳定方案,防范血管额外损伤风险。

[**关键词**] 残余胆固醇炎症指数;变异性;卒中

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Variability of remnant cholesterol inflammation index exhibits a dose-response relationship with stroke risk: Evidence from the Chinese Kailuan cohort

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[**Abstract**] Objective To investigate the association between the variability of remnant cholesterol inflammatory index (RCII), a novel composite biomarker, and the risk of stroke, in order to provide a theoretical basis for stroke prevention. Methods A prospective cohort study was conducted on 38 659 Kailuan individuals who took annual physical examinations in 2006, 2008, and 2010. These subjects were grouped based on the quartiles of RCII variability, which was represented by standard deviation (SD) and average real variability (ARV), and were followed up every 2 years, with the occurrence of stroke (including ischemic and hemorrhagic strokes), death, or the end of follow-up on December 31, 2022 as the endpoints. Kaplan-Meier method was used to calculate the cumulative incidence rate of endpoint events across different groups, and log-rank test was used to compare the difference of cumulative incidence of endpoint events in each group. Multivariate Cox proportional hazards regression model was adopted to analyze the association between RCII variability and risk of stroke. Results Among the 38 659 participants, a total of 2 539 strokes occurred during a mean follow-up period of 11.22±2.26 years. After adjusting confounding factors, when the participants were grouped by the quartiles of RCII-SD, the hazard ratio (HR) for stroke was 1.034 (95%*CI*: 0.917~1.167, *P*=0.584), 1.146 (95%*CI*: 1.018~1.290, *P*=0.025), and 1.209 (95%*CI*: 1.066~1.370, *P*=0.003), respectively in the Q2, Q3, and Q4 groups, when compared with the Q1 group (P_{trend} <0.05). When they were grouped by the quartiles of RCII-ARV, the HR for stroke was 1.008 (95%*CI*: 0.894~1.136, *P*=0.901), 1.109 (95%*CI*: 0.986~1.248, *P*=0.085), and 1.152 (95%*CI*: 1.018~1.303, *P*=0.025), respectively, in the Q2, Q3, and Q4 groups, when compared with the Q1 group. Furthermore, both sensitivity and stratified analyses yielded similar results. Conclusion RCII variability is significantly associated with stroke, and the risk of stroke is gradually increasing with increment of the variability. Countermeasures Relevant authorities can focus on reducing RCII variability as a central objective by establishing regular monitoring mechanism, strengthening lifestyle interventions, and standardizing dietary, exercise, and weight management in order to suppress the index fluctuations. The principle of stable lipid-lowering in medication and optimization of therapeutic regimens with stable efficacy should be emphasized to prevent the risk of additional vascular damage.

[**Key words**] remnant cholesterol inflammatory index; variability; stroke

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卒中是一种急性脑血管疾病,具有高发病率、高患病率及高死亡率的特点,是全球范围内重大公共卫生问题[1]。2021年,全球卒中发病率为150/10万人年,患病率为1 180/10万人年,死亡率为每92/10万人年[2]。在我国,>65岁的人群中男性卒中发病率为2 875/10万人年,女性卒中发病率为1 839/10万人年[3]。因此,早期识别卒中的危险因素以降低其发病率和患病率至关重要。

残余胆固醇(remnant cholesterol,RC)是指富含甘油三酯(triglyceride,TG)的脂蛋白(包括极低密度脂蛋

白和中间密度脂蛋白)中的胆固醇成分[4-5]。研究发现,RC每增加一个标准差,卒中的风险将会增加6%[6]。RC不仅是动脉粥样硬化的关键驱动因素,还能通过促炎机制加速血管损伤[7]。一项来自哥本哈根的研究表明,RC与高敏C反应蛋白(high-sensitivity C-reactive protein,hs-CRP)联合使动脉粥样硬化性心脏病的发生风险增加了1.9倍[8]。因此,本研究引入RCII,RCII是一种整合了RC和hs-CRP的新指数,将RC与hs-CRP单位统一后相乘,量化血脂和炎症的协同效应[9-10],能够更全面的评估卒中的发生风险。一项来自CHARLS数据库的研究表明,RCII每增加1个标准差,卒中的发生风险增加10.6%,高于单独的RC或hs-CRP对卒中的发生风险[9]。然而,尚缺乏研究证明RCII的变异性与卒中发生风险的关联,因此,本研究基于开滦队列研究(注册号:ChiCTR-TNRC-11001489),探讨RCII的变异性与卒中的关联,为卒中的预防提供参考。

1 研究方法与对象

1.1 研究对象

本研究选取连续参加2006年度、2008年度、2010年度的开滦健康体检者和问卷调查者(n=58 869)为研究对象,同意并签署知情同意书。排除标准:①高密度脂蛋白胆固醇(high density lipoprotein cholesterol,HDL-C)、低密度脂蛋白胆固醇(low density lipoprotein cholesterol,LDL-C)、总胆固醇(total cholesterol,TC)、hs-CRP数据缺失者(n=18 317);②既往卒中病史者(n=1 893),最终纳入38 659名观察对象。本研究遵照赫尔辛基宣言,并获得开滦总医院伦理委员会批准[(2006)医伦字5号]。

1.2 资料收集

1.2.1 一般资料收集 研究人群的人口学特征、一般资料、实验室检查及研究设计的详细信息参照本课题组已发表的文献[11]。体检者于体检当日需空腹8 h,由专业人员抽取肘静脉血5 mL于EDTA真空管内,在室温下经3 000 r/min离心10 min后取上层血清进行生化指标检测,hs-CRP、TC、HDL-C和LDL-C采用酶比色法进行测定,根据公式RC=TC-HDL-C-LDL-C;RCII=RC×hs-CRP计算RCII的值[9,12]。并使用2006年度、2008年度、2010年度3次体检所测得的RCII的标准差(standard deviation,SD)[13]和平均真实变异性(average real variability,ARV)[14]来定义RCII的变异性

1.2.2 相关指标定义 脑卒中的诊断由二级及以上医院专科医师根据世界卫生组织定义的诊断标准:存在局灶性运动神经功能障碍的症状体征,经影像学检查(头颅MRI/CT)确诊为脑卒中(包括缺血性脑卒中和出血性脑卒中)[15]。

吸烟定义为近1年平均每天至少吸1支烟,连续吸烟1年以上。饮酒定义为近1年平均每日饮酒(酒精含量50%以上)100 mL,连续饮酒1年以上。高血压定义为收缩压≥140 mmHg和(或)舒张压≥90 mmHg,或收缩压<140 mmHg和舒张压<90 mmHg但有高血压病史或正在服用降压药[16];糖尿病定义为空腹血糖≥7.0 mmol/L或空腹血糖<7.0 mmol/L但有糖尿病病史或正在服用降糖药[17];高脂血症定义为TC≥6.2 mmol/L或HDL-C<1.0 mmol/L或LDL-C≥4.1 mmol/L或TG≥2.3 mmol/L或有高血脂病史或正在服用降脂药[18]。体育锻炼定义为每周锻炼≥3次,每次持续时间至少30 min。肾小球滤过率(estimated glomerular filtration rate,eGFR)采用慢性肾脏病学流行病学合作研究公式法计算(CKD-EPI)[19]。

1.2.3 随访和终点事件 以完成2010年度体检的时间为随访起点,以发生卒中(包括缺血性卒中和出血性卒中)、死亡或随访结束(2022年12月31日)为随访终点,共计38 659名观察对象完成了平均(11.22±2.26)年的随访。

1.3 统计学分析

采用SAS 9.4软件进行统计分析。符合正态分布的计量资料采用$\bar{x}\pm s$表示,组间比较采用方差分析;非正态分布的计量资料采用$M(P_{25},P_{75})$表示,组间比较采用非参数秩和检验(Kruskal-Wallis);计数资料用例(%)来表示,组间比较采用χ^2检验;以事件数除以随访总人年(1 000/人年)分别计算不同RCII的变异性组别发生卒中的发病密度,采用Kaplan-Meier法计算不同分组发生终点事件的累积发病率,组间比较采用Log-Rank检验;采用多因素Cox比例风险回归模型分别分析RCII的变异性不同分组对终点事件的发生风险及95%CI,以P<0.05(双侧检验)为差异有统计学意义。模型一校正年龄、性别;模型二在模型一的基础上校正吸烟、饮酒、体质指数(body Mass Index,BMI)、体育锻炼、高血压、糖尿病、高血脂、eGFR、打鼾、降压药、降糖药、降脂药;模型三在模型二的基础上校正2010年的RCII;模型四在模型二的基础上校正2006年的RCII。

2 结果

2.1 以RCII-SD四分位分组的一般资料比较

在该项研究中,男性29 318名(占75.8%),女性9 341名(占24.2%),年龄(53.2±11.8)岁。与Q1组相比,Q4组研究对象的年龄、TC、hs-CRP、RC、BMI、RCII较高,且患高血压、糖尿病、高血脂的人数较多,服用

降压药、降糖药、降脂药的人数也较多(P<0.001),见表1。

2.2 RCII的变异性与卒中的累积发生率

在中位随访11.94年期间,共发生了2 539例卒中事件,发病密度为5.85/千人年(95%*CI*:5.63~6.09)。其中,缺血性卒中发生2 313例,出血性卒中发生302例。以RCII-SD四分位分组,Q1组~Q4组分别发生卒中495例(5.12%)、579例(5.99%)、668例(6.91%)、797例(8.25%),4组发病密度分别为4.49(4.11~4.91)/千人年、5.29(4.88~5.74)/千人年、6.17(5.72~6.65)/千人年、7.53(7.03~8.07)/千人年。各组间累积发病率差异有统计学意义($P_{log\text{-}rank}$<0.05);见图1。

2.3 RCII的变异性与卒中的多因素Cox比例风险回归分析

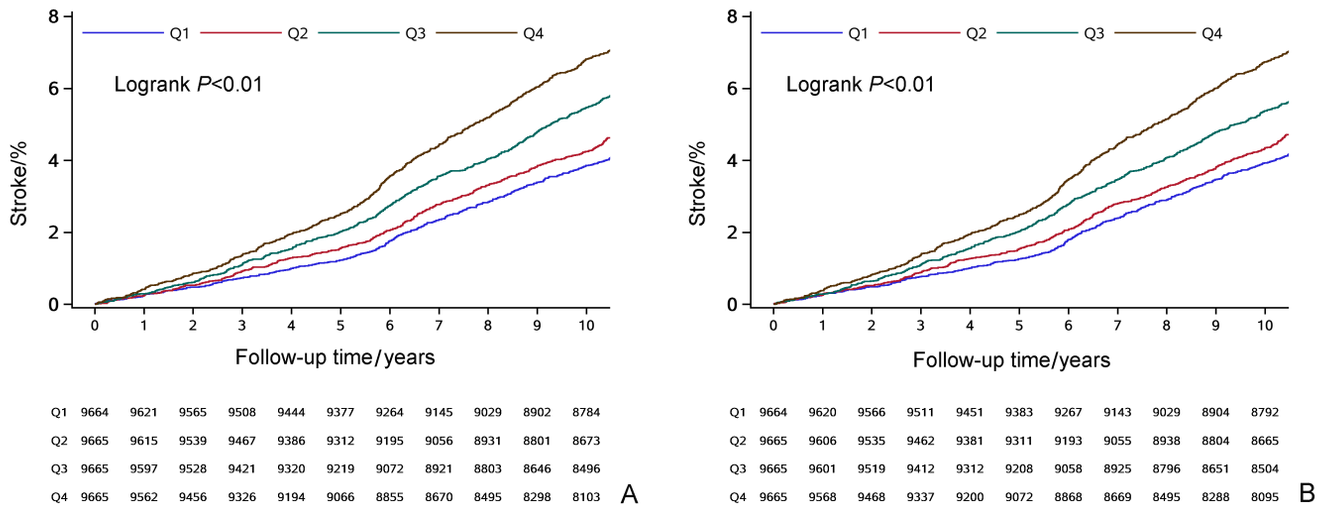
以RCII-SD四分位分组为自变量,与Q1组相比,

表1 不同RCII-SD分组研究对象的基线特征[$\bar{x}\pm s$,例(%),$M(P_{25},P_{75})$]

Table 1 Baseline characteristics of the participants grouped according to the quartiles of RCII-SD [$\bar{x}\pm s$, n(%), $M(P_{25},P_{75})$]

Factors	Total (n=38 659)	Q1 (n=9 664)	Q2 (n=9 665)	Q3 (n=9 665)	Q4 (n=9 665)	P value
RCII-SD/(mmol/L)	3.9(1.5~10.0)	0.8(0.5~1.1)	2.5(2.0~3.1)	6.0(4.9~7.6)	20.3(13.5~35.7)	<0.001
Age/years	53.2±11.8	51.5±11.8	52.6±11.6	53.3±11.6	55.6±11.7	<0.001
Male	29 318(75.8)	7 205(74.6)	7 466(77.2)	7 425(76.8)	7 222(74.7)	<0.001
Total cholesterol/(mmol/L)	5.1±1.1	4.8±0.9	5.1±0.9	5.2±1.0	5.3±1.3	<0.001
Low density lipoprotein cholesterol/(mmol/L)	2.6±0.8	2.6±0.7	2.7±0.7	2.7±0.8	2.5±1.0	<0.001
High density lipoprotein cholesterol/(mmol/L)	1.5(1.2~1.8)	1.6(1.3~1.9)	1.5(1.3~1.8)	1.4(1.2~1.8)	1.4(1.2~1.7)	<0.001
Remnant cholesterol/(mmol/L)	0.7(0.4~1.3)	0.5(0.3~0.8)	0.7(0.4~1.1)	0.7(0.4~1.3)	1.1(0.5~2.0)	<0.001
Remnant cholesterol/(mg/dL)	26.7(15.1~49.1)	18.6(12.0~30.9)	25.9(15.5~43.3)	28.6(16.2~48.7)	42.9(20.5~77.3)	<0.001
hs-CRP/(mg/L)	1.3(0.7~2.9)	0.7(0.4~1.2)	1.2(0.7~2.1)	1.8(0.9~3.3)	2.9(1.2~5.9)	<0.001
hs-CRP/(mg/dL)	0.1(0.1~0.3)	0.1(0.0~0.1)	0.1(0.1~0.2)	0.2(0.1~0.3)	0.3(0.1~0.6)	<0.001
eGFR/[mL/(min·1.73 m^2)]	91.0±19.4	92.2±19.4	91.5±19.9	91.2±18.7	89.2±19.3	<0.001
Current smoker	13 216(34.2)	3 077(31.8)	3 367(34.8)	3 545(36.7)	3 227(33.4)	<0.001
Current drinker	13 864(35.9)	3 417(35.4)	3 646(37.7)	3 678(38.1)	3 123(32.3)	<0.001
Physical activity	5 620(14.5)	1 394(14.4)	1 372(14.2)	1 450(15.0)	1 404(14.5)	0.442
Snorer	15 750(40.7)	3 608(37.3)	4 078(42.2)	4 334(44.8)	3 730(38.6)	<0.001
BMI/(kg/m^2)						<0.001
Normal/underweight(<24)	15 515(40.1)	4 997(51.7)	3 913(40.5)	3 441(35.6)	3 164(32.7)	
Overweight (24~<28)	16 145(41.8)	3 680(38.1)	4 101(42.4)	4 223(43.7)	4 141(42.8)	
Obese (≥28)	6 999(18.1)	987(10.2)	1 651(17.1)	2 001(20.7)	2 360(24.4)	
Hypertension	17 763(45.9)	3 623(37.5)	4 450(46.0)	4 621(47.8)	5 069(52.4)	<0.001
Diabetes	4 307(11.1)	626(6.5)	923(9.5)	1 177(12.2)	1 581(16.4)	<0.001
Hyperlipemia	13 294(34.4)	2 007(20.8)	3 094(32.0)	3 840(39.7)	4 353(45.0)	<0.001
Antihypertensive drugs	7 227(18.7)	1 242(12.9)	1 694(17.5)	1 975(20.4)	2 316(24.0)	<0.001
Hypoglycemic drugs	2 327(6.0)	363(3.8)	482(5.0)	628(6.5)	854(8.8)	<0.001
Lipid-lowering drugs	879(2.3)	131(1.4)	198(2.0)	210(2.2)	340(3.5)	<0.001
$RCII_{2010}$	3.7(1.4~9.4)	1.5(0.7~2.6)	3.9(1.6~6.1)	6.2(1.9~12.3)	12.1(3.4~32.6)	<0.001
$RCII_{2008}$	4.8(1.9~11.7)	1.7(0.9~2.8)	4.3(2.2~6.5)	9.5(3.8~14.3)	16.7(6.0~32.4)	<0.001
$RCII_{2006}$	2.9(0.9~9.6)	1.1(0.4~2.3)	2.4(0.8~5.4)	4.3(1.3~11.5)	20.9(4.1~52.1)	<0.001
RCII-ARV	4.8(1.8~12.7)	1.0(0.6~1.4)	3.0(2.3~4.0)	7.7(5.7~10.2)	25.8(17.5~44.2)	<0.001

RCII: Remnant cholesterol inflammatory index; SD: Standard deviation; hs-CRP: High-sensitivity C-reactive protein; eGFR: Estimated glomerular filtration rate; ARV: Average real variability



A: RCII-SD cumulative incidence rate curve for new-onset stroke; B: RCII-ARV cumulative incidence rate curve for new-onset stroke. RCII: Remnant cholesterol inflammatory index; SD: Standard deviation; ARV: Average real variability

图 1 不同 RCII 变异性水平对新发卒中事件的累积发病率曲线

Figure 1 Cumulative incidence of new-onset stroke in different variabilities of RCII

表 2 RCII 的变异性与卒中发病风险的 Cox 比例回归分析

Table 2 Association between RCII variability and risk of stroke in the participants by Cox proportional hazards regression analysis

Factors	Event/Total	Incidence density	HR (95% *CI*)			
			Model 1	Model 2	Model 3	Model 4
RCII-SD						
Q1	495/9 664	4.49	Ref.	Ref.	Ref.	Ref.
Q2	579/9 665	5.29	1.135(1.007~1.280)	1.037(0.919~1.170)	1.034(0.917~1.167)	1.037(0.919~1.171)
Q3	668/9 665	6.17	1.299(1.157~1.460)	1.153(1.025~1.298)	1.146(1.018~1.290)	1.156(1.027~1.301)
Q4	797/9 665	7.53	1.470(1.313~1.645)	1.241(1.105~1.394)	1.209(1.066~1.370)	1.258(1.105~1.431)
P_{trend}			<0.0001	<0.0001	0.0008	0.0001
Per SD increase			1.094(1.059~1.130)	1.056(1.021~1.093)	1.043(1.000~1.087)	1.081(1.028~1.136)
RCII-ARV						
Q1	510/9 664	4.63	Ref.	Ref.	Ref.	Ref.
Q2	576/9 665	5.26	1.097(0.974~1.236)	1.011(0.897~1.139)	1.008(0.894~1.136)	1.011(0.897~1.140)
Q3	667/9 665	6.16	1.263(1.125~1.417)	1.119(0.995~1.258)	1.109(0.986~1.248)	1.119(0.995~1.259)
Q4	786/9 665	7.42	1.396(1.249~1.562)	1.189(1.060~1.334)	1.152(1.018~1.303)	1.192(1.049~1.354)
P_{trend}			<0.0001	0.0006	0.0083	0.0021
Per SD increase			1.089(1.055~1.125)	1.055(1.020~1.091)	1.041(1.001~1.083)	1.062(1.018~1.108)

Model 1 was adjusted for age and sex; Model 2 was adjusted for variables in model 1 and smoking, alcohol consumption, body mass index, physical activity, diabetes, hypertension, hyperlipemia, eGFR, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs; Model 3 was adjusted for variables in model 2 and RCII in 2010; Model 4 was adjusted for variables in model 2 and RCII in 2006. RCII: Remnant cholesterol inflammatory index; SD: Standard deviation; ARV: Average real variability; eGFR: Estimated glomerular filtration rate; Ref: Reference; HR: Hazard ratio; CI: Confidence interval. The incidence density is per 1 000 person-years.

较高的 RCII 的变异性能增加卒中的发生风险。校正年龄、性别、吸烟、饮酒、体育锻炼、BMI、eGFR、高血压、糖尿病、高血脂、打鼾、降压药、降糖药、降脂药、2010 年的 RCII 后，Q2~Q4 组发生卒中的 HR 值为 1.034(95%*CI*：0.917~1.167)、1.146(95%*CI*：1.018~1.290)和 1.209(95%*CI*：1.066~1.370)，P_{trend}<0.05，RCII-SD 每增加一个标准差，卒中的发生风险增加 4%；见表 2。此外，以 RCII-ARV 四分位分组为自变量，结果与 RCII-SD 结果类似，见表 2。同时，以 RCII-SD、RCII-ARV 四分位分组分别对缺血性卒中和出血性卒中进行了 Cox 回归分析，结果显示，随着 RCII-SD、RCII-ARV 的增加，Q2~Q4 组发生缺血性卒中和出血

性卒中的风险均增加,见表3、4。

2.4 RCII的变异性与卒中的关联的敏感性分析

为保证结果的稳健性,分别以RCII-SD、RCII-ARV为自变量,卒中为因变量进行了敏感性分析:①排除随访1年内即发生卒中的人群(n=264);②排除心肌梗死、房颤、癌症病史的人群(n=1 209);③排除使用降脂药的人群(n=1 507)。校正相关协变量后,结果未发生显著变化。此外,使用Fine-Gray模型进行死亡竞争风险分析与主要结果分析类似,见表5。

2.5 RCII的变异性与卒中的关联的分层分析

分别以年龄(<60岁,≥60岁)、性别(男,女)进行了分层分析,校正相关协变量后,RCII的变异性与卒中的关联在年龄、性别中没有显著交互作用($P_{interaction}$>0.05),但在年龄<60岁、女性中关联更显著,见表6。

2.6 基于均值的RCII与卒中的多因素Cox比例风险回归分析

为保证结果的稳健性,进行了基于均值的RCII与卒中的Cox回归分析。校正相关混杂因素后,与Q1组相比,较高的RCII能增加卒中的发生风险。此外,分别对缺血性卒中和出血性卒中进行了Cox回归分析,结果显示,随着RCII的增加,Q2~Q4组发生缺血性卒中和出血性卒中的风险均增加;但在出血性卒中中结果无统计学意义,见表7。

3 讨论

本研究发现,随着RCII的变异性增加,卒中发生风险也随之增加,且独立于单次测量值。RCII的变异性与缺血性卒中的关联更显著。RCII的变异性与卒中的关联受年龄、性别的影响。

与既往研究相比,本研究首次探讨了RCII的变异性与卒中的关联,随着RCII变异性的升高,卒中的发生风险也随之升高。既往来自CHARLS数据库的研究首次提出了RCII这个指标,该研究表明,高RC能使卒中的发生风险增加1.7倍,较高的hs-CRP能使卒中的发生风险增加1.4倍,而RCII能使卒中的发生风险增加1.9倍[9],表明RC与炎症指标联合能更好地预测卒中的发生。一项来自哥本哈根的研究也发现了类似的结论,该研究表明,与RC和hs-CRP双低组相比,RC与hs-CRP双高组能使动脉粥样硬化性心脏病的发生风险增加1.9倍[8]。XIONG等[20]也发现RC与hs-CRP双高组能使卒中的发生风险增加1.7倍。本研究

表3 RCII的变异性与缺血性卒中的关联的Cox比例回归分析

Table 3 Associations between RCII variability and risk of ischemic stroke in the participants by Cox proportional hazards regression analysis

Factors	Event/Total	Incidence density	HR (95% *CI*)			
			Model 1	Model 2	Model 3	Model 4
RCII-SD						
Q1	453/9 664	4.10	Ref.	Ref.	Ref.	Ref.
Q2	519/9 665	4.73	1.111(0.980~1.260)	1.005(0.886~1.141)	1.002(0.883~1.138)	1.006(0.886~1.142)
Q3	611/9 665	5.63	1.299(1.150~1.467)	1.136(1.004~1.285)	1.126(0.994~1.275)	1.138(1.006~1.289)
Q4	730/9 665	6.88	1.472(1.309~1.656)	1.221(1.081~1.378)	1.177(1.032~1.342)	1.240(1.083~1.419)
P_{trend}			<0.0001	0.0001	0.0036	0.0004
Per SD increase			1.094(1.057~1.132)	1.053(1.016~1.092)	1.033(0.989~1.079)	1.076(1.021~1.134)
RCII-ARV						
Q1	461/9 664	4.17	Ref.	Ref.	Ref.	Ref.
Q2	525/9 665	4.79	1.106(0.976~1.254)	1.011(0.892~1.147)	1.007(0.888~1.142)	1.011(0.892~1.147)
Q3	607/9 665	5.60	1.272(1.127~1.435)	1.111(0.982~1.257)	1.099(0.971~1.244)	1.112(0.983~1.258)
Q4	720/9 665	6.78	1.417(1.260~1.594)	1.187(1.052~1.339)	1.139(1.001~1.297)	1.192(1.043~1.362)
P_{trend}			<0.0001	0.0013	0.0205	0.0036
Per SD increase			1.091(1.055~1.129)	1.054(1.018~1.092)	1.036(0.993~1.080)	1.062(1.016~1.110)

Model 1 was adjusted for age and sex; Model 2 was adjusted for variables in model 1 and smoking, alcohol consumption, body mass index, physical activity, diabetes, hypertension, hyperlipemia, eGFR, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs; Model 3 was adjusted for variables in model 2 and RCII in 2010; Model 4 was adjusted for variables in model 2 and RCII in 2006. RCII: Remnant cholesterol inflammatory index; SD: Standard deviation; ARV: Average real variability; eGFR: Estimated glomerular filtration rate; Ref: Reference; HR: Hazard ratio; CI: Confidence interval. The incidence density is per 1 000 person-years

表4 RCII的变异性与出血性卒中的关联的Cox比例回归分析

Table 4 Associations between RCII variability and risk of hemorrhagic stroke in the participants by Cox proportional hazards regression analysis

Factors	Event/Total	Incidence density	HR (95% *CI*)			
			Model 1	Model 2	Model 3	Model 4
RCII-SD						
Q1	56/9 664	0.50	Ref.	Ref.	Ref.	Ref.
Q2	73/9 665	0.65	1.262(0.891~1.788)	1.240(0.873~1.760)	1.249(0.880~1.774)	1.242(0.875~1.764)
Q3	81/9 665	0.73	1.375(0.978~1.933)	1.385(0.980~1.958)	1.416(1.000~2.005)	1.395(0.986~1.974)
Q4	92/9 665	0.85	1.466(1.050~2.047)	1.451(1.030~2.044)	1.577(1.091~2.279)	1.520(1.039~2.226)
P_{trend}			0.0237	0.0292	0.0120	0.0234
Per SD increase			1.081(0.982~1.190)	1.074(0.974~1.184)	1.112(0.996~1.242)	1.131(0.986~1.297)
RCII-ARV						
Q1	64/9 664	0.57	Ref.	Ref.	Ref.	Ref.
Q2	66/9 665	0.59	0.998(0.707~1.407)	0.985(0.697~1.392)	0.991(0.701~1.401)	0.986(0.698~1.394)
Q3	82/9 665	0.74	1.222(0.881~1.695)	1.222(0.877~1.704)	1.244(0.890~1.738)	1.227(0.879~1.713)
Q4	90/9 665	0.83	1.246(0.903~1.720)	1.227(0.882~1.708)	1.304(0.916~1.857)	1.257(0.870~1.816)
P_{trend}			0.0957	0.1191	0.0712	0.1197
Per SD increase			1.064(0.966~1.172)	1.056(0.957~1.165)	1.082(0.971~1.206)	1.072(0.948~1.212)

Model 1 was adjusted for age and sex; Model 2 was adjusted for variables in model 1 and smoking, alcohol consumption, body mass index, physical activity, diabetes, hypertension, hyperlipemia, eGFR, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs; Model 3 was adjusted for variables in model 2 and RCII in 2010; Model 4 was adjusted for variables in model 2 and RCII in 2006. RCII: Remnant cholesterol inflammatory index; SD: Standard deviation; ARV: Average real variability; eGFR: Estimated glomerular filtration rate; Ref: Reference; HR: Hazard ratio; CI: Confidence interval. The incidence density is per 1 000 person-years

进一步探讨了RCII的变异性对卒中的发生风险,减少了单次测量时存在的混杂因素,表明高RCII的变异性能增加卒中的发生风险,并分别校正了2010年的RCII和2006年的RCII,结果并未发生显著变化,表明RCII的变异性可能是卒中的独立危险因素。因此,未来的研究不仅要关注RCII的绝对水平,更应关注其波动情况。

RC是指富含TG的脂蛋白胆固醇成分,包括空腹状态下的极低密度脂蛋白胆固醇和中间密度脂蛋白胆固醇以及非空腹状态下的乳糜微粒[21],相比LDL-C,RC能够能好的预测卒中的发生风险。CUI等[22]用CHNS数据库和CHARLS数据库均得出,即使具有最佳LDL-C水平,升高的RC也能增加卒中的发生风险。一项来自哥本哈根的研究发现,在缺血性心脏病的发生中,与LDL-C相比,RC与炎症反应的关系更密切[23]。在卒中的发生发展中,RC与hs-CRP相互作用,加速血管损伤[24]。ZHANG等[25]发现RC与hs-CRP在动脉粥样硬化疾病中存在相互中介作用,CHEN等[9]发现RC占hs-CRP和卒中之间中介作用的10.5%,而hs-CRP占RC和卒中之间中介作用的3.3%。因此,相比单一指标,将二者联合探讨可能避免低估卒中的残余风险。一项来自CHARLS数据库的研究表明,RCII每增加一个标准差,卒中的发生风险增加10.6%,且该研究发现高累积RCII也能促进卒中的发生[9]。本研究进一步探讨了其长期的波动性与卒中的关联,这种波动性可能提示炎症反应和氧化应激的反复出现,这种反复损伤会导致血管内皮功能持续受损。虽然既往尚无研究直接探讨RCII的变异性与卒中的关联,但有研究表明RC的变异性能增加卒中的发生风险,该研究表明,RC的变异性每增加一个标准差,缺血性卒中的发生风险增加9%,且最高四分位人群风险增加27%[26]。RCII是整合血脂指标和炎症指标的新指数,其波动性能更好地反映血脂及炎症对血管损伤的严重程度,预测价值优于单独的血脂波动性。

RCII的变异性与缺血性卒中的关联优于出血性卒中。缺血性卒中和出血性卒中在病因、病理机制上存在显著差异,前者多与动脉粥样硬化及血栓形成相关,而后者则主要由血管壁受损导致。在缺血性卒中的发生发展中,血脂异常和炎症有着至关重要的作用,与LDL-C不同,RC颗粒更大,虽然其进入动脉内膜的速度相对较慢,但更容易被“困”在其中,进而被巨噬细胞摄取形成泡沫细胞,导致内皮细胞功能障碍并

表5 RCII的变异性与卒中的关联的敏感性分析

Table 5 Sensitivity analysis for the association between RCII variability and risk of stroke

Factors	*HR* (95% *CI*)				P_{trend}	Per SD increase
	Q1	Q2	Q3	Q4		
RCII-SD						
Sensitivity analysis 1(*n*=38 395)	Ref.	1.046 (0.924~1.183)	1.160 (1.027~1.310)	1.220 (1.073~1.388)	0.0007	1.040 (0.997~1.086)
Sensitivity analysis 2(*n*=37 450)	Ref.	1.011 (0.894~1.144)	1.127 (0.998~1.272)	1.184 (1.041~1.346)	0.0026	1.027 (0.983~1.073)
Sensitivity analysis 3(*n*=37 152)	Ref.	1.048 (0.926~1.186)	1.147 (1.016~1.296)	1.224 (1.076~1.392)	0.0008	1.061 (1.008~1.097)
Sensitivity analysis 4(*n*=38 659)	Ref.	1.034 (0.917~1.167)	1.146 (1.018~1.290)	1.209 (1.066~1.370)	<0.0001	1.043 (1.000~1.087)
RCII-ARV						
Sensitivity analysis 1(*n*=38 395)	Ref.	1.018 (0.900~1.151)	1.128 (1.000~1.272)	1.172 (1.032~1.329)	0.0043	1.043 (1.001~1.085)
Sensitivity analysis 2(*n*=37 450)	Ref.	1.001 (0.886~1.132)	1.108 (0.982~1.250)	1.137 (1.001~1.290)	0.0161	1.027 (0.985~1.071)
Sensitivity analysis 3(*n*=37 152)	Ref.	1.028 (0.910~1.162)	1.113 (0.986~1.256)	1.168 (1.029~1.327)	0.0074	1.047 (1.006~1.090)
Sensitivity analysis 4(*n*=38 659)	Ref.	1.008 (0.894~1.136)	1.109 (0.986~1.248)	1.152 (1.018~1.303)	0.0083	1.041 (1.001~1.083)

Sensitivity analysis 1: Exclude individuals with new-onset cases within first 1 years of follow-up; Sensitivity analysis 2: Exclude individuals who experienced myocardial infarction or atrial fibrillation or cancer history; Sensitivity analysis 3: Exclude individuals who had ever used lipid-lowering medications. Sensitivity analysis 4: Competing risk regression to address mortality related confounding. Model was adjusted for age, sex, smoking, alcohol consumption, body mass index, physical activity, diabetes, hypertension, hyperlipemia, eGFR, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs, and RCII in 2010. RCII: Remnant cholesterol inflammatory index; SD: Standard deviation; ARV: Average real variability; eGFR: Estimated glomerular filtration rate; Ref: Reference; HR: Hazard ratio; CI: Confidence interval

表6 RCII的变异性与卒中的关联的分层分析

Table 6 Stratified analysis for the associations between RCII variability and risk of stroke

Factors	$P_{interaction}$	HR (95% *CI*)				P_{trend}	Per SD increase
		Q1	Q2	Q3	Q4		
RCII-SD							
Age<60	0.41	Ref.	1.109(0.950~1.294)	1.156(0.989~1.351)	1.385(1.173~1.636)	0.000 2	1.067(1.007~1.131)
Age≥60		Ref.	0.955(0.786~1.161)	1.188(0.988~1.429)	1.140(0.941~1.381)	0.045 5	1.053(0.994~1.116)
Female	0.07	Ref.	1.106(0.780~1.568)	1.319(0.941~1.850)	1.564(1.115~2.195)	0.003 6	1.053(0.954~1.162)
Male		Ref.	1.023(0.899~1.163)	1.121(0.987~1.273)	1.151(1.005~1.319)	0.017 6	1.040(0.994~1.089)
RCII-ARV							
Age<60	0.13	Ref.	1.035(0.887~1.208)	1.157(0.993~1.348)	1.339(1.138~1.576)	0.000 2	1.068(1.014~1.126)
Age≥60		Ref.	0.996(0.823~1.204)	1.106(0.919~1.330)	1.079(0.893~1.303)	0.280 0	1.046(0.988~1.107)
Female	0.02	Ref.	1.300(0.921~1.835)	1.111(0.783~1.576)	1.775(1.271~2.478)	0.001 3	1.063(0.965~1.170)
Male		Ref.	0.969(0.853~1.102)	1.111(0.980~1.259)	1.060(0.927~1.212)	0.135 5	1.038(0.994~1.084)

Model was adjusted for age, sex, smoking, alcohol consumption, body mass index, physical activity, diabetes, hypertension, hyperlipemia, eGFR, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs, and RCII in 2010. RCII: Remnant cholesterol inflammatory index; SD: Standard deviation; ARV: Average real variability; eGFR: Estimated glomerular filtration rate; Ref: Reference; HR: Hazard ratio; CI: Confidence interval

加剧血管内皮损伤[27-28]。此外,泡沫细胞还可释放炎症介质,促进黏附分子聚集,引发炎症反应及凝血级联反应,从而进一步推动动脉粥样硬化斑块的形成[29]。相反,出血性卒中通常源于高血压性脑动脉破

表7 均值RCII与卒中及其亚型发病风险的Cox比例回归分析

Table 7 Cox proportional regression analysis of mean RCII and risk of stroke and its subtypes

Factors	Event/Total	Incidence density	*HR* (95% *CI*)			
			Model 1	Model 2	Model 3	Model 4
Stroke						
Q1	462/9 664	4.17	Ref.	Ref.	Ref.	Ref.
Q2	575/9 665	5.25	1.166(1.031~1.318)	1.063(0.939~1.203)	1.061(0.937~1.200)	1.064(0.940~1.204)
Q3	691/9 665	6.40	1.372(1.219~1.544)	1.182(1.047~1.335)	1.175(1.040~1.327)	1.186(1.050~1.339)
Q4	811/9 665	7.69	1.568(1.397~1.759)	1.263(1.119~1.425)	1.228(1.076~1.402)	1.284(1.121~1.472)
P_{trend}			<0.001	<0.001	<0.001	<0.001
Per SD increase			1.118(1.082~1.154)	1.063(1.027~1.101)	1.056(1.006~1.109)	1.117(1.055~1.183)
Ischemic Stroke						
Q1	411/9 664	3.70	Ref.	Ref.	Ref.	Ref.
Q2	522/9 665	4.75	1.190(1.046~1.355)	1.075(0.944~1.225)	1.072(0.941~1.222)	1.076(0.945~1.227)
Q3	637/9 665	5.86	1.423(1.257~1.612)	1.206(1.061~1.370)	1.195(1.051~1.359)	1.209(1.064~1.375)
Q4	743/9 665	7.03	1.618(1.433~1.827)	1.276(1.124~1.450)	1.227(1.068~1.411)	1.302(1.128~1.502)
P_{trend}			<0.001	<0.001	0.001	<0.001
Per SD increase			1.124(1.087~1.162)	1.065(1.028~1.104)	1.051(0.999~1.106)	1.126(1.061~1.194)
Hemorrhagic Stroke						
Q1	60/9 664	0.53	Ref.	Ref.	Ref.	Ref.
Q2	575/9 665	0.67	1.162(0.827~1.632)	1.154(0.819~1.626)	1.164(0.826~1.641)	1.157(0.821~1.631)
Q3	73/9 665	0.66	1.094(0.777~1.540)	1.100(0.775~1.564)	1.127(0.792~1.606)	1.111(0.781~1.580)
Q4	94/9 665	0.87	1.360(0.982~1.884)	1.326(0.942~1.868)	1.464(1.004~2.134)	1.405(0.962~2.074)
P_{trend}			0.092	0.140	0.075	0.138
Per SD increase			1.044(0.943~1.157)	1.028(0.925~1.142)	1.077(0.931~1.245)	1.032(0.860~1.240)

Model 1 was adjusted for age and sex; Model 2 was adjusted for variables in model 1 and smoking, alcohol consumption, body mass index, physical activity, diabetes, hypertension, hyperlipemia, eGFR, snoring, antihypertensive, lipid-lowering and glucose-lowering drugs; Model 3 was adjusted for variables in model 2 and RCII in 2010; Model 4 was adjusted for variables in model 2 and RCII in 2006. RCII: Remnant cholesterol inflammatory index; SD: Standard deviation; ARV: Average real variability; eGFR: Estimated glomerular filtration rate; Ref: Reference; HR: Hazard ratio; CI: Confidence interval. The incidence density is per 1 000 person-years

裂或脑血管结构异常,其核心机制是血管壁的完整性被破坏,而非RC所主导的粥样斑块堵塞过程[30]。HAN等[6]基于China-PAR队列研究也发现了类似的结果,该研究表明RC与缺血性卒中呈正相关,而与出血性卒中无关。

RCII的变异性与卒中的关联在中青年人群、女性中更显著,既往开滦研究在探讨RC的变异性与缺血性卒中的关联中也发现了类似的结论[26]。相比男性,女性体内RC与hs-CRP的关联优于男性,这可能会进一步放大卒中的残余风险[23]。WANG等[10]使用CHARLS数据库观察RCII与全因死亡的关联时发现在女性中这种关联更明显,但性别分层无显著交互作用。因此,更早期的降低RCII的波动性至关重要。在药物方面,他汀类药物已证明不仅有降脂作用,也有抗炎作用[15,31-32],但能否降低其整体的波动性还有待商榷。因此,未来的药物研究不仅应考虑能否降低其绝对水平,更应该关注其波动性,平稳降脂,以免对心血管造成额外损伤。

本研究首次证明了RCII的变异性与卒中显著相关,其次,尽可能地排除相关混杂因素,进行敏感性分析及分层分析以提高结果的可靠性。局限性:本研究为观察性研究,可能无法明确RCII的变异性与卒中之间关联的机制,需要在以后的研究中得以确认。其次,该研究仅使用了两个变异性指标,未来的研究需要考虑更多的变异性指标。

将RCII纳入卒中高危人群的筛查指标,对于RCII升高但无卒中病史者,加强其生活方式的干预,必要时采用药物干预,对于卒中病史者,建议在降脂的同

时抗炎治疗,实现“脂质-炎症”双路径控制,平稳降脂,降低卒中的发病及复发风险。

基于开滦队列研究,本课题组发现RCII的变异性与卒中发生风险有显著相关性,随着RCII的变异性的增加,卒中的发生风险也随之增加。

利益冲突 本文所有作者声明不存在利益冲突

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