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Low cholesterol levels are associated with a high mortality risk in older adults without statins therapy: An externally validated cohort study

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ABSTRACT

Background: The relationship of total cholesterol (TC) levels with mortality among older adults without statin therapy has not been fully studied.
Aims: To examine the relationship between TC and all-cause mortality in adults aged 65 years and older in Russia without statin therapy.
Methods: This was a population-based prospective cohort study of community-dwelling people aged 65 years and older in Russia. Data from 379 individuals on cardiovascular risk factors; comorbidities; cognitive, physical and autonomous function; lipid panel; B-type natriuretic peptide; C-reactive protein; and others were collected through interviews, clinical examinations, and laboratory tests. The total follow-up time was 3 years. Cox proportional hazards models for all-cause mortality, C-statistics, internal validation and external validation using the Belgian population from the BELFRAIL study were performed.
Results: A U-shaped association between the TC level and all-cause mortality was identified. Older adults without statin therapy and with low/high TC levels were at higher risk for mortality even after adjustment for covariates, with a hazard ratio (HR) of 5.78 (1.96–17.03) for TC < 5.4 mmol/L and an HR of 6.24 (1.69–22.94) for TC levels > 7.2 mmol/L. The association between low TC and all-cause mortality was confirmed in an external population of adults 80 years and older.
Conclusion: The TC level range associated with the lowest mortality was 5.4–7.2 mmol/L, irrespective of concomitant diseases or health status. The association between low TC levels and a high risk of all-cause mortality was confirmed in a Belgian cohort of adults 80 years and older.

1. Introduction

Dyslipidaemia is a major risk factor for cardiovascular disease and mortality (Jellinger et al., 2017). Therefore, reducing cholesterol levels is an integral component of the recommendations for preventing cardiovascular disease and mortality (Jellinger et al., 2017; Yi, Yi, & Ohrr, 2019). Age, however, seems to weaken the relative effect of total cholesterol (TC) on cardiovascular mortality (Cabrera, de Andrade, & Dip, 2012; Hamazaki, Okuyama, Ogushi, & Hama, 2013; Liang, Vetrano, & Qiu, 2017; Nago, Ishikawa, Goto, & Kayaba, 2011; Newson et al., 2011; Ravnskov et al., 2016; Schatz et al., 2001; Takata et al., 2014; Tuikkala et al., 2010; Yi et al., 2019). Several studies have shown no association between the prevalence of cardiovascular diseases (CVDs) and TC levels in older individuals (Li, Du et al., 2018; Nagasawa et al., 2012; Takata et al., 2014; Tuikkala et al., 2010), while other studies have confirmed the associations of high TC levels with CVD and mortality (Prospective Studies Collaboration et al. (2007)). Moreover, although the most recent meta-analysis of 28 randomized controlled trials showed that statin therapy led to a reduction in major vascular events irrespective of age, it revealed no direct evidence of benefit among patients older than 75 years who do not already have evidence of occlusive vascular disease (Armitage et al., 2019).

Several studies have conversely shown that low TC and low-density lipoprotein (LDL) levels are negatively related to all-cause mortality,

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cancer and haemorrhagic stroke in older individuals, which can be explained by the decreased platelet activity associated with hypocholesterolaemia (Cabrera et al., 2012; Liang et al., 2017; Ma et al., 2019; Ravnskov et al., 2016; Schatz et al., 2001; Takata et al., 2014; Tuikkala et al., 2010; Wang, Dong, Qi, Huang, & Hou, 2013; Weverling-Rijnsburger, Jonkers, van Exel, Gussekloo, & Westendorp, 2003). The findings of the Leiden 85-Plus Study revealed that low LDL was mostly associated with a 3-fold increased mortality risk due to infection, whereas the risk of mortality from CVD and cancer was not increased (Weverling-Rijnsburger et al., 2003).

Russia combines the features of developed and developing countries, with a high mortality rate from CVD, which resembles developed countries, and low overall life and healthy life expectancy, as seen in developing countries. However, despite the similar prevalence of risk factors such as high blood pressure, hypercholesterolemia, and diabetes, Russia has a lower use of statin therapy than other developed countries (Bhatt et al., 2006; Kotseva et al., 2009; Martsevich, Tripkosh, Lukina, & Zagrebel'nyy, 2013). There was an almost threefold difference between countries according to the results of different cross-sectional studies of patients with coronary heart disease: 25.4–66 % in Russia compared to 88.6 % in Belgium or 95.4 % in Finland (Kotseva et al., 2009; Martsevich et al., 2013). The ESSE-RF study of community-dwelling people aged 25–64 years old from 13 regions in Russia detected even lower adherence to statin therapy (Boytsov S.A., 2014). The ESSE-RF study showed that 31.3 % of participants had a high and very high risk of CVD, but only 7.0 % of them received statins (Boytsov et al., 2014; Shalnova et al., 2016). Given these characteristics of the Russian population, this paper aims to examine the relationship between cholesterol levels and all-cause mortality in community-dwelling adults aged 65 years and older in Russia and to perform an internal and external validation of the observed results.

2. Materials and methods

Data were derived from the prospective population-based Crystal study of community-dwelling adults aged 65 years and older. The study participants were randomly selected from one of the districts of Saint-Petersburg, Russia.

2.1. Ethical considerations

The local ethics committee of The Northwestern State Medical University named after I.I. Mechnikov approved the study protocol (protocol №1, from 22.01.2014)

2.2. Data collection

The study design and objectives have been previously described in detail (Gurina, Frolova, & Degryse, 2011). The initial cohort consisted of 611 people aged 65–91 years (Fig. 1). The data from the second assessment were collected 2.5 years later. A total of 379 people participated in the second assessment since 102 participants died before the second assessment and 130 patients refused to participate. According to the results of the first assessment, the baseline characteristics of those 130 who refused were similar to the 379 who participated in the second assessment (Turusheva, Frolova, Hegendoerfer, & Degryse, 2017). As a wider spectrum of laboratory tests was performed in the second assessment than in the first, including a lipid panel for all participants, the current analysis is based on information from the second assessment. The mean duration of the follow-up of mortality was 26.1 ± 6.1 months (Table 1).

2.3. Study parameters

- Laboratory tests. Lipid panel, B-type natriuretic peptide (BNP), thyroid-stimulating hormone (TSH), C-reactive protein (CRP), and creatinine were determined using a Roche Cobas Integra 400 analyser and an Architect i1000 System. The target level for LDL was chosen as < 3 mmol/L (Mach et al., 2019). The cut-off of TSH was 3.2 UI/mL. The cut-off of CRP used to define high CRP was > 5 mg/L for both sexes. Haemoglobin levels were determined using the cyanide-free haemoglobinometry method on an Abbott Cell-Dyn3700 haematology analyser. The cut-off of haemoglobin levels used to define anaemia was < 130 g/L for men and < 120 g/L for women. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease formula (Stevens et al., 2007). A GFR < 60 mL/min indicated a decline in renal function. The cut-off used for high BNP (hBNP) was > 100 pg/mL.
- Details of past and current medical problems and medication use were collected based on anamnesis and information presented in the medical records.
- The modified version of the Short Physical Performance Battery (SPPB) that was used consists of timed measurements of the following activities: quick walking, rising from a chair, putting on and taking off a cardigan, and maintaining balance in a tandem standing position. The cut-off value for poor physical performance was defined as an SPPB score < 8 (Turusheva et al., 2017).
- The 15-item Geriatric Depression Scale (GDS-15) was used to screen for depressive symptoms. The cut-off value for depression was defined as a score equal to or greater than 5 (de Craen, Heeren, & Gussekloo, 2003).
- The Mini-Mental State Examination (MMSE) was used to identify cognitive impairment. The cut-off score was less than 24 (Tombaugh & McIntyre, 1992).
- The Barthel Index (BI) of activities of daily living was used to determine the baseline level of functioning and the consequent degree of dependence. The cut-off for dependency was defined as a score of less than 95.
- Nutritional status was evaluated using the Mini Nutritional Assessment (MNA) questionnaire. An MNA score < 23.5 indicated malnutrition or risk for malnutrition.

2.4. Outcomes

The mortality status of the participants from baseline through September 19, 2014 was determined using the National Death Registry. There was no loss to follow-up for the mortality assessment.

2.5. External validation

The BELFRAIL study (BFc80+) is a prospective, observational, population-based cohort study of people aged 80 years and older living in Belgium. The study protocol and sampling methods have already been described (Vaes et al., 2010). In brief, between November 2008 and September 2009, 567 individuals were included in the study. Only three exclusion criteria were used: known severe dementia, palliative situations, and medical urgency. Data on total cholesterol levels were obtained from 550 individuals. The total follow-up time for mortality was 3 years. The date and cause of mortality were obtained from the detailed follow-up questionnaires from the general practitioners of the participants. There was no loss to follow-up for mortality. Unlike the Crystal study, high-sensitivity C-reactive protein (hs-CRP) with a cut-off value of 0.3 mg/L was used as a component of the combination of anaemia and hs-CRP (Vaes et al., 2010).

2.6. Data analyses

Descriptive statistics were calculated for baseline and outcome variables. Continuous data are presented as the median (Me) and interquartile range [IQR]. Differences between the participants were compared using the Mann–Whitney U-test, and independent samples were compared with the Kruskal-Wallis test or chi-squared tests.

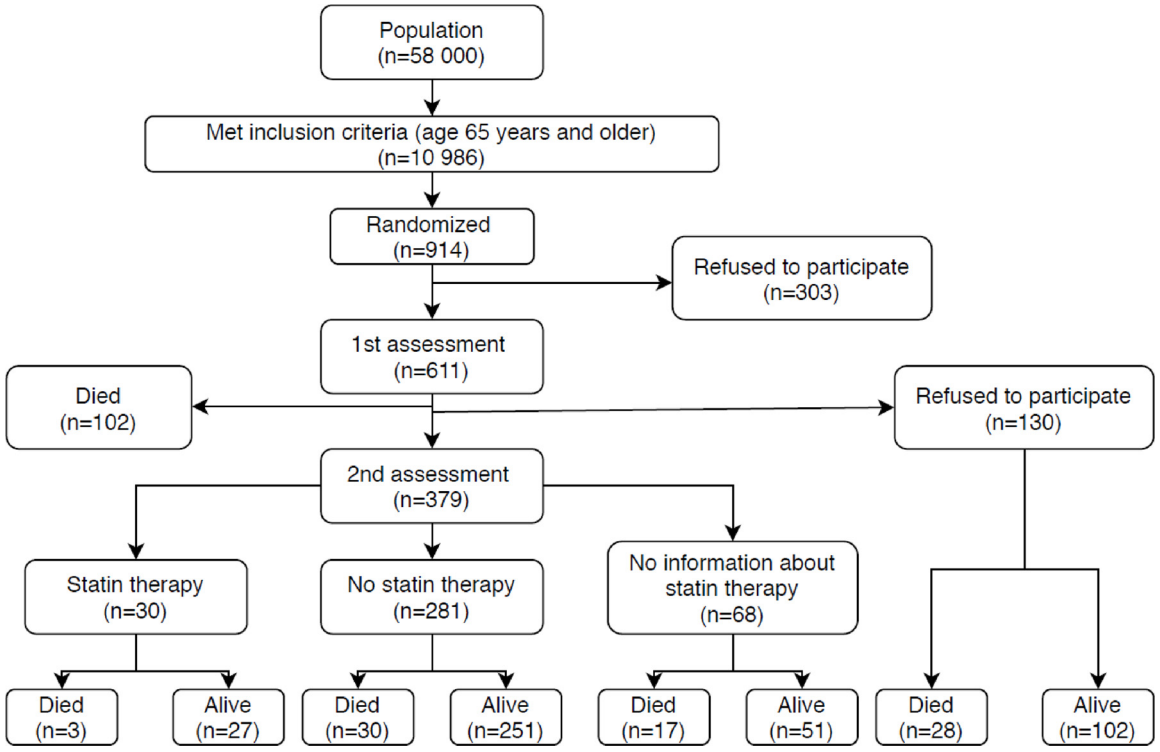

Fig. 1. Flowchart of data collection in the Crystal cohort study.

Kaplan-Meier curves and log-rank tests were used to assess the relationship with mortality, and log-rank was used to compare different strata. Cox proportional hazard regression models (adjusted for age, sex and comorbidities) were used to estimate hazard ratios (HRs) for mortality. Models were checked for the proportional hazard assumption. In the case of multicollinearity (r-value > 0.80), only one of the two covariables was considered in the multivariable model. The CHAID algorithm, adjusted for survival, was used to determine the value for TC levels associated with low mortality risk in our population (Hadizadeh, Rahnama, & Hesari, 2019). Harrell's C-index concordance statistic was used to measure the predictive quality of models [38]. A zone of uncertainty was also calculated for the models to test the relative predictive accuracy using a jackknife procedure (internal validation) (Newson, 2010).

External validation was performed using Kaplan-Meier curve analysis, log-rank test, Cox proportional hazard regression models and Harrell's C-index.

All statistical calculations were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and IBM SPSS Modeler 14.2 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Participants

The present study included 379 participants with a median age of 76 [IQR: 72.0–81.0] years, of whom 75.1 % (n = 284) were women (Fig. 1).

The morbidity burden was high: 95.5 % of the participants had more than one disease, and 21.7 % suffered from ≥5 chronic diseases. In total, 81.5 % of participants had high blood pressure, 20.6 % had a history of stroke, 19.0 % had atrial fibrillation and 15.8 % had a history of myocardial infarction. In addition, there was a high prevalence of depression (40.9 %), cognitive impairment (34.0 %), risk of malnutrition (36.0 %), anaemia (26.3 %), dependency (17.7 %) and physical decline (45.6 %).

Data about medications were obtained from 311 participants. A total of 20.9 % of participants were not taking any drugs, 30.5 % of participants were taking β-blockers, 17.4 % were taking angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, 13.2 % were taking calcium channel blockers and 18.6 % were taking diuretics. Statin therapy was prescribed only for 9.7 % of participants. The most commonly used statins were atorvastatin and simvastatin. More often, statins and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers were used by people with higher education (university) and those who lived with partners or children. There were no differences in other medications according to educational level or type of living situation.

The levels of TC and LDL in the statin therapy group were significantly lower than those in the without statin therapy group (Table 1). However, the target levels of LDL were achieved in 50 % of the participants on statins. Participants from the statin therapy group were younger and had better cognitive function and a higher education level but more often had a history of myocardial infarction and higher CRP and BNP levels (Table 1). Those participants without information about statin therapy (n = 68) displayed a higher prevalence of depression, were more dependent on external assistance, had a lower grip strength and had a higher likelihood of malnutrition than those in the statin therapy group (Table 1).

3.2. Association between TC levels and mortality

Using backward stepwise Cox regression analysis, we found that high TC levels were negatively associated with all-cause mortality in the total population and appeared to be a stronger factor than high/low LDL and low high-density lipoprotein (HDL) levels after adjustment for age and sex [HR (95 % CI) = 0.73 (0.56 − 0.95)].

Participants without statin therapy were assessed to determine the levels of TC that were associated with low mortality in older adults. According to the chi-square automatic interaction detection (CHAID) algorithm adjusted for survival, we detected a U-shaped association between all-cause mortality and TC levels. The lowest all-cause

Table 1
Health characteristics of the Crystal cohort population.

	Statin group (n = 30)	Without statin therapy (n = 281)	Without information about statin therapy (n = 68)
Age, n [IQR]*	72.5 [71.0–79.0]*	76.0 [72.0–80.0]	80.0 [76.0–85.0]
Men, n (%)	10 (33.3)	68 (24.3)	16 (23.5)
Education level, n (%)			
Primary	5 (16.7)	79 (28.1)	24 (35.3)
Secondary	16 (53.3)	163 (58.0)	36 (52.9)
Higher*	9 (30.0)*	39 (13.9)	8 (11.8)
Type of living situation, n (%)			
Institutionalized	–	–	–
Alone at home	7 (23.3)	93 (33.1)	22 (32.4)
With partner at home	10 (33.3)	68 (24.2)	13 (19.1)
With children at home	13 (43.3)	114 (40.6)	28 (41.2)
Other	–	6 (2.1)	5 (7.4)
Arterial hypertension, n (%)	25 (83.3)	227 (80.8)	57 (83.8)
Myocardial infarction, n (%)*	8 (26.7)*	26 (9.3)	10 (14.7)
Stroke, n (%)	5 (16.7)	37 (13.2)	15 (22.1)
Atrial fibrillation, n (%)	8 (26.7)	53 (18.9)	10 (14.7)
Diabetes mellitus, n (%)	8 (26.7)	44 (15.7)	14 (20.6)
COPD, n (%)	7 (23.3)	51 (18.2)	9 (13.2)
Anaemia, n (%)	7 (23.3)	70 (25.2)	21 (30.9)
GDS ≥5, n (%)	11 (36.7)	102 (36.3)	42 (61.8)*
SPPB < 8, n (%)	12 (40.0)	155 (55.6)	39 (58.2)
Index Barthel < 95, n (%)	5 (16.7)	33 (11.8)	28 (41.2)*
MNA ≤ 23.5, n (%)	10 (33.3)	92 (33.0)	33 (55.0)*
MMSE < 24, n (%)*	3 (10.0)*	91 (32.5)	50 (34.0)
TSG > 3.2 μU/mL, n (%)	6 (20.0)	65 (23.2)	12 (17.6)
CRP > 5, n (%)*	12 (40.0)*	53 (19.0)	18 (26.5)
TC, mmol/L [IQR]*	5.30 [4.25–5.87]*	5.72 [5.03–6.56]	5.4 [4.60–6.49]
LDL, mmol/L [IQR]*	3.31 [2.57–3.77]*	3.67 [3.01–4.32]	3.68 [2.79–4.23]
Triglycerides, mmol/L [IQR]	1.45 [0.98–1.87]	1.28 [0.95–1.73]	1.20 [0.85–1.66]
HDL, mmol/L [IQR]	1.25 [0.98–1.51]	1.34 [1.13–1.59]	1.17 [0.98–1.47]
BNP > 100, n (%)	11 (36.7)	68 (24.3)	20 (29.4)
GFR < 60 mL/min, n (%)	7 (23.0)	42 (15.0)	10 (14.7)

*p < 0.05.

mortality risk was observed in participants with TC levels between 5.4 and 7.2 mmol/L.

The main baseline characteristics of the Crystal study population according to statin therapy and TC levels are shown in Table 2.

Participants with TC levels < 5.4 mmol/L or > 7.2 mmol/L displayed a fivefold higher mortality risk in the next 2.5 years than participants with total cholesterol levels between 5.4 and 7.2 mmol/L (Figs. 2, 3, Table 3).

This difference remained significant for low TC levels even after adjustment for age, sex, education level, type of living situation, cognition function, atrial fibrillation, CRP, BNP, nutritional status, cancer and anaemia, with an HR of 5.78 (1.96–17.03). For TC levels > 7.2 mmol/L in the group without statin therapy, the HR was 6.24 (1.69–22.94). The same association between TC levels and mortality was found in the total population, with an HR (95 % CI) of 4.87 (1.79 -13.27) for TC levels < 5.4 mmol/L and 5.23 (1.50–18.28) for TC levels > 7.2 mmol/L (Table 3).

3.3. Internal validation

After bootstrapping, Harrell's C (95 % CI) value was 0.66 (0.60 – 0.73) for low TC levels and 0.59 (0.48 – 0.70) for high TC levels in the total population of the Crystal study and 0.69 (0.60 – 0.78) for low TC levels and 0.67 (0.52 − 0.82) for high TC levels in the group without statin therapy.

3.4. External validation

The BELFRAIL cohort consisted of 550 participants with an average age of 84.0 [IQR 81.7–86.6] years, of whom 62.8 % were females. The morbidity burden was high in the BELFRAIL population. Nevertheless, BELFRAIL cohort participants had a better nutritional status; lower prevalence of cognitive impairment, depression, and anaemia; and more often lived with partners but had higher CRP levels than participants in the Crystal cohort. However, the proportion of people with low autonomy and higher education levels who lived with children was higher in the Crystal population.

Follow-up data for all-cause mortality were available for all of the BELFRAIL participants. During the first 3 years of follow-up, 127 (23.0 %) participants died.

Data about statin therapy were available from 548 participants. In total, 31.9 % of participants (n = 180) had been prescribed statins. Participants in the statin therapy group were younger; were more likely to live with partners; and had a higher prevalence of anaemia, angina pectoris, diabetes mellitus, and history of myocardial infarction but a lower prevalence of depression.

We did not observe a significant association between TC and mortality risk in the total population. Nevertheless, Kaplan-Meier survival curves showed that all-cause mortality at the 3-year follow-up was significantly higher in participants without statin therapy and with TC levels < 5.4 mmol/L than in participants with TC levels of 5.4–7.2 mmol/L (log-rank test p = 0028) (Fig. 4). Participants with low TC levels without statin therapy had a higher prevalence of anaemia and higher hs-CRP levels, as was found in the Crystal study (Table 4). Statistically, no significant difference was found in other health characteristics across different TC levels in the BELFRAIL cohort (Table 4).

The association between low TC levels and all-cause mortality remained significant, even after adjustment for age, sex, education level, type of living situation, cognitive function, atrial fibrillation, CRP, BNP, nutritional status, and cancer (HR (95 % CI) = 1.94 (1.05–3.58)), but the association disappeared after adjusting for anaemia (Table 5).

4. Discussion

4.1. Main findings

In the Crystal study, we discovered a U-shaped association between TC levels and mortality. TC levels between 5.4 and 7.2 mmol/L were associated with a lower risk of all-cause mortality than lower or higher TC levels. The association between low TC levels and a higher risk of all-cause mortality was confirmed in a Belgian cohort of adults aged 80 years and older.

4.2. Interpretation of findings in relation to previously published studies and features of the Russian population

The Russian population has a Western lifestyle with high intake of processed meat, butter, sweets, fried foods, refined grains and high-sugar drinks; sedentary lifestyles; and a high prevalence of obesity and noncommunicable diseases (Petrukhin & Lunina, 2011). Additionally, Russia has a lack of necessary medical care, lower socioeconomic status, lower overall life expectancy and lower healthy life expectancy than developed countries. The closest European country to Saint-Petersburg is Finland. The average life expectancy in neighbouring

Table 2
Health characteristics of the Crystal cohort participants with different total cholesterol levels according to statin use.

	Statin group n = 29		Without statin group n = 280		
	< 5.4 mmol\L n = 16	5.4–7.2 mmol\L n = 13	< 5.4 mmol\L n = 106	5.4–7.2 mmol\L n = 143	> 7.2 mmol\L n = 31
Age, years [IQR]*	72.0 [70.2–3.2]*	73.0 [71.5–79.0]	76.0 [72.0–81.2]	75.0 [72.0–80.0]	77.0 [72.0–80.0]
Male, n (%)	6 (37.5)	4 (30.8)	36 (34.0)	29 (20.3)	3 (9.7)
Education level, n (%)					
Primary*	1 (6.3)	4 (30.8)	41 (38.7)*	30 (21.0)	7 (22.6)
Secondary/college*	10 (62.5)	6 (46.2)	50 (47.2)*	93 (65.0)	20 (64.5)
University	5 (31.3)	3 (23.1)	15 (14.2)	20 (14.0)	4 (12.9)
Type of living status, n (%)					
Institutionalized	–	–	–	–	–
Alone at home	6 (37.5)	1 (7.7)	36 (34.0)	47 (32.9)	10 (32.3)
With partner at home	4 (25.0)	6 (46.2)	29 (27.4)	34 (23.8)	5 (16.1)
With children at home	6 (37.5)	6 (46.2)	38 (35.8)	60 (42.0)	15 (48.4)
Other	–	–	3 (2.8)	2 (1.4)	1 (3.2)
Arterial hypertension, n (%)	14 (87.5)	10 (76.9)	79 (74.5)	123 (86.0)	24 (77.4)
Myocardial infarction, n (%)	4 (25.0)	4 (30.8)	18 (17.0)	18 (12.6)	4 (12.9)
Stroke, n (%)	2 (25.0)	2 (15.4)	19 (17.9)	26 (18.2)	9 (29.0)
Atrial fibrillation, n (%)*	5 (31.3)	3 (23.1)	28 (26.4)*	20 (14.0)	6 (19.4)
Diabetes mellitus, n (%)	5 (31.3)	3 (23.1)	19 (17.9)	30 (21.0)	9 (29.0)
COPD, n (%)	5 (31.3)	1 (7.7)	21 (19.8)	23 (16.1)	7 (22.6)
Peripheral arterial disease, n (%)	7 (43.8)	4 (30.8)	7 (6.6)	32 (22.4)	9 (29.0)
Cancer, n (%)	–	2 (15.4)	4 (3.8)	7 (4.9)	2 (6.5)
Anaemia, n (%)*	5 (31.3)	2 (15.4)	28 (26.4)*	27 (18.9)	8 (26.7)
GDS > 5, n (%)	3 (18.8)	5 (38.5)	35 (33.3)	34 (23.8)	9 (29.0)
SPPB < 8, n (%)	4 (25.0)	7 (53.8)	29 (27.4)	81 (57.0)	22 (71.0)
Index Barthel < 95, n (%)	2 (12.5)	3 (23.1)	13 (12.3)	17 (11.9)	3 (9.7)
MNA ≤ 23.5, n (%)*	5 (31.3)	5 (38.5)	40 (38.1)*	37 (26.1)	14 (45.2)
MMSE < 24, n (%)*	1 (6.3)	2 (15.4)	32 (30.2)	46 (32.2)	13 (41.9)*
TSG > 3.2 μU/mL, n (%)	3 (18.8)	3 (23.1)	24 (22.6)	34 (23.8)	7 (22.6)
CRP > 5 g/L, n (%)*	7 (43.8)	5 (38.5)	25 (23.6)*	24 (16.9)	4 (12.9)
BNP > 100 pg/mL, n (%)*	9 (56.3)*	1 (7.7)	33 (31.4)*	28 (19.6)	7 (22.6)
GFR < 60 mL/min, n (%)	6 (37.5)	1 (7.7)	12 (11.3)	23 (16.1)	7 (22.6)

*p < 0.05.

Finland is 78.7 years for men and 84.4 years for women (https://www.stat.fi). The average life expectancy in Saint-Petersburg is 69.8 years for men and 78.7 years for women, and the cardiovascular mortality rate is threefold higher in Saint-Petersburg than in neighbouring Finland (Kotseva et al., 2009; Martsevich et al., 2013). Moreover, the observed high mortality rate in our study in the Crystal cohort was comparable to the official age-specific death data in Russia – 26.2 deaths per 1000 people aged 65–69 years, 39.1 deaths per 1000 people aged 70–74 years, 58.2 deaths per 1000 people aged 75–79 years, 96.7 deaths per 1000 people aged 80–85 years and 171.5 deaths per 1000 people aged 85 years and older (Statistical Digest of Russia, 2015). Nonetheless, the discovered association between all-cause mortality and TC levels

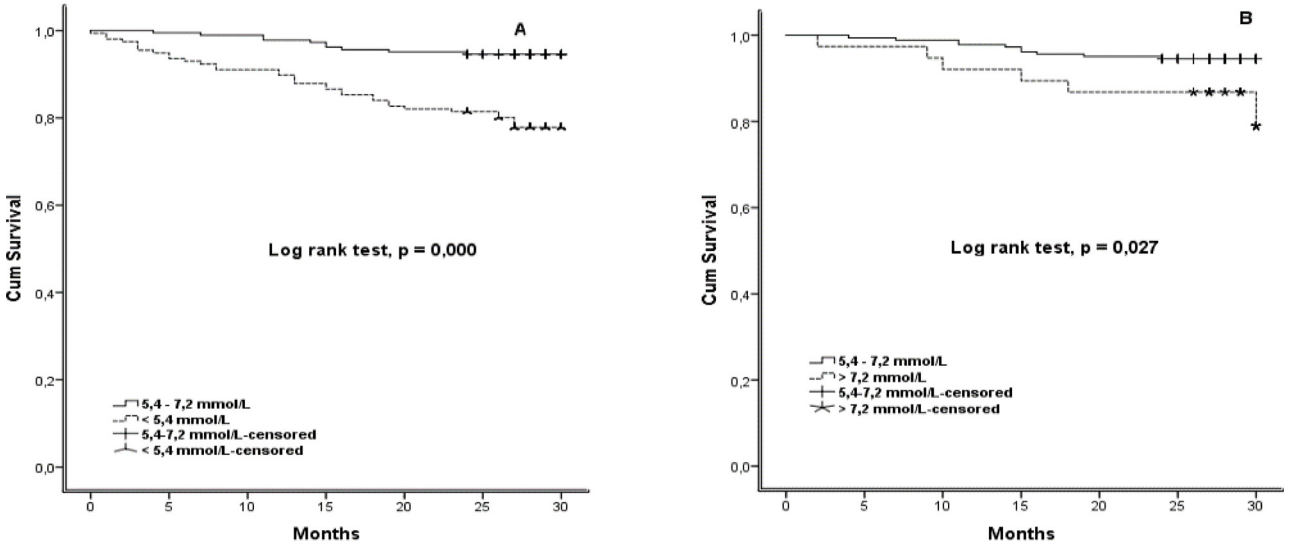

Fig. 2. Kaplan-Meier curves for all-cause 2.5 - year mortality in the Crystal cohort (n = 379) based on total cholesterol levels.
A – comparison between the groups with cholesterol levels between 5.4 and 7.2 mmol/L and < 5.4 mmol/L.
B – comparison between the groups with cholesterol levels between 5.4 and 7.2 mmol/L and > 7.2 mmol/L.

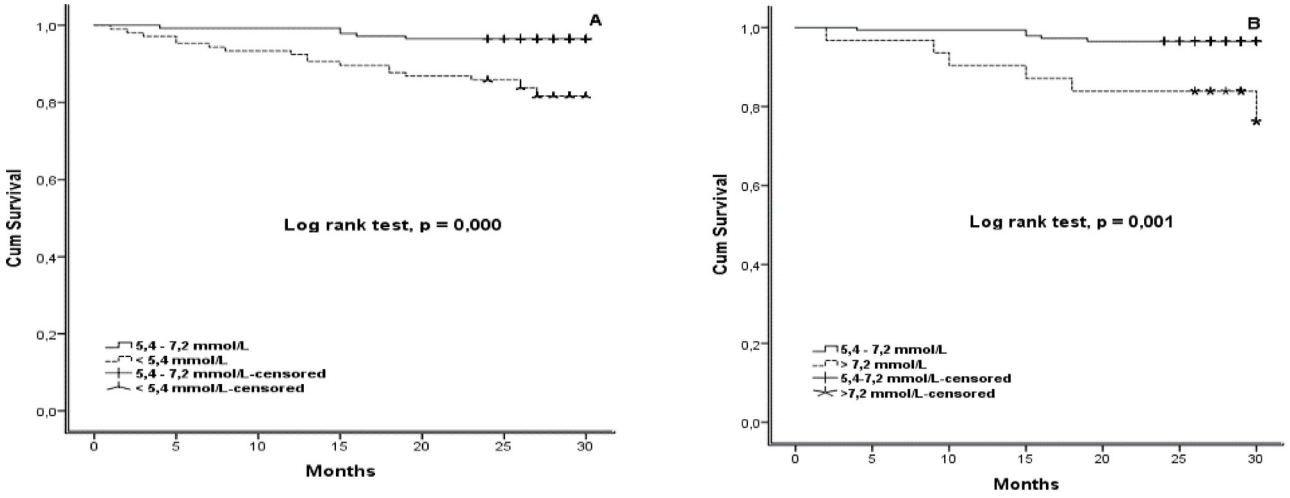

Fig. 3. Kaplan-Meier curves for all-cause 2.5 - year mortality in the Crystal cohort (n = 280) without statin therapy based on total cholesterol levels.
A – comparison between the groups with cholesterol levels between 5.4 and 7.2 mmol/L and < 5.4 mmol/L.
B – comparison between the groups with cholesterol levels between 5.4 and 7.2 mmol/L and > 7.2 mmol/L.

corresponded with the results obtained in other European populations (Liang et al., 2017; Tuikkala et al., 2010).

In the current study, we found that TC levels between 5.4 and 7.2 mmol/L were associated with a lower risk of all-cause mortality. This reference range is consistent with data from the SNAC-K study (Sweden) and the Kuopio 75 health study (Finland), where TC levels of 5.18–6.21 mmol/l and 5.0–5.9 mmol/l, respectively, were associated with lower all-cause mortality in older adults (Liang et al., 2017; Tuikkala et al., 2010). Both studies were conducted in Nordic countries with similar climate zones and nutrition patterns similar to those in Saint-Petersburg but with higher life expectancy and income.

The U-shaped association between TC and all-cause mortality was also found in the Korean Metabolic Risk Factor (KOMERIT) study, which included more than 12 million participants aged 18–99 years. TC levels between 210 and 249 mg/dL (5.43–6.44 mmol/L) were associated with the lowest all-cause mortality rate in both sexes and almost all age groups (Hamazaki et al., 2013).

We performed external validation of the obtained results on a Western European population with other eating habits, better social-economic status, other types of living situations, other educational levels and higher life and healthy life expectancy than in Russia. However, the low TC level was associated with a high risk of all-cause mortality in the BELFRAIL study even after adjustment for all covariates.

We found no association between high TC and high risk of mortality in the BELFRAIL study that can be linked with survival effect. This result was confirmed in the Leiden 85+ study of community-dwelling older adults 85 years and older (Weverling-Rijnsburger et al., 2003).

4.3. Possible interconnection between TC level and mortality in older adults

The association between low TC levels and mortality in the ageing population is poorly understood. The decrease in TC levels in older adults could be linked with the presence of serious diseases, frailty, systemic inflammation, malnutrition and/or cancer (Liu et al., 2018). Furthermore, in the current study, the prevalence of anaemia, malnutrition, and high CRP and BNP levels was higher in participants with low levels of TC. However, even after adjusting for all these conditions, the association between all-cause-mortality and low TC levels remained significant. In other studies, low TC levels were also found to be an

Table 3
Assessment of mortality risk by the cholesterol levels in the Crystal study.

	Total population			Without statin therapy		
	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
5.4 – 7.2 mmol/L	1	1	1	1	1	1
< 5.4 mmol/L	**4.45 (2.20 – 9.01)**	**3.96 (1.94 – 8.09)**	**4.87 (1.79 – 13.27)**	**5.74 (2.14 – 15.39)**	**5.23 (1.94 – 14.13)**	**5.78 (1.96 – 17.03)**
> 7.2 mmol/L	**3.07 (1.11 – 8.44)**	**2.99 (1.07 – 8.33)**	**5.23 (1.50 – 18.28)**	**6.14 (1.87 – 20.12)**	**6.24 (1.88 – 20.74)**	**6.24 (1.69 – 22.94)**
Age		1.18 (1.12 – 1.24)	1.17 (1.09 – 1.26)		1.20 (1.12 – 1.29)	1.14 (1.06 – 1.23)
Sex		2.47 (1.31 – 4.67)	2.92 (1.27 – 6.73)		2.92 (1.29 – 6.60)	2.95 (1.24 – 7.04)
Educational levels		0.99 (0.65 – 1.51)	1.20 (0.70 – 2.07)		1.14 (0.66 – 1.97)	1.34 (0.75 – 2.40)
Current family situation		1.20 (0.91 – 1.58)	1.38 (0,92 –2.06)		1.36 (0.92 – 2.00)	1.35 (0.88 – 2.05)
Statins			1.54 (0.40 – 6.00)			–
hs–CRP > 0.3			2.65 (1.16 – 6.03)			3.49 (1.45 – 8.38)
BNP < 100			2.15 (0,99 – 4.65)			2.74 (1.20 – 6.23)
MNA < 23.5			2.16 (0.99 – 4.72)			2.48 (1.09 – 5.62)
MMSE < 24			2.42 (1.06 – 5.53)			2.42 (1.01 – 5.79)
Atrial fibrillation			0.68 (0.31 – 1.49)			0.62 (0.27 – 1.42)
Cancer			1.15 (0.23 – 5.75)			2.39 (0.49 – 11.73)
Anaemia			1.12 (0.49 – 2.52)			0.98 (0.41 – 2.36)
For total cholesterol levels < 5.4 mmol/L:				**For total cholesterol levels < 5.4 mmol/L:**		
Harrell's C (95% CI) - 0.66 (0.60 – 0.73)				Harrell's C - 0.69 (0.60 – 0.77)		
For total cholesterol levels > 7.2 mmol/L:				**For total cholesterol levels > 7.2 mmol/L:**		
Harrell's C (95% CI) - 0.66 (0.60 – 0.73)				Harrell's C (95% CI) - 0.73 (0.56 – 0.89)		

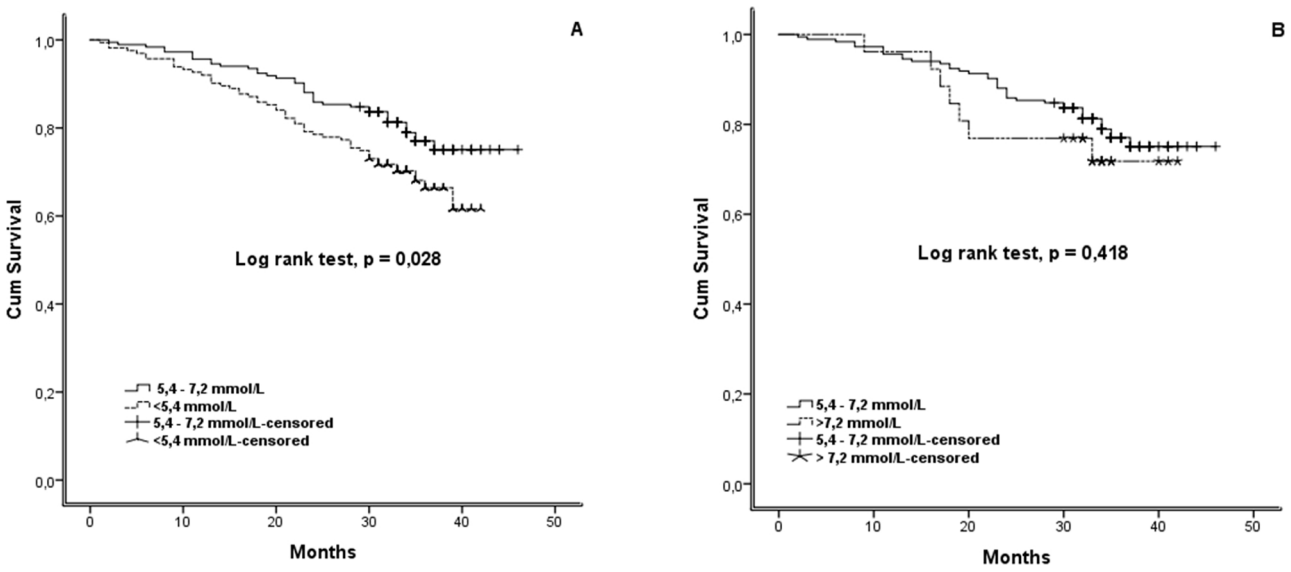

Fig. 4. Kaplan-Meier curves for all-cause 3-year mortality in the BELFRAIL cohorts (n = 365) without statin therapy based on total cholesterol levels A – comparison between the groups with cholesterol levels between 5.4 and 7.2 mmol/L and < 5.4 mmol/L B - comparison between the groups with cholesterol levels between 5.4 and 7.2 mmol/L and > 7.2 mmol/L.

Table 4
Health characteristics of the BELFRAIL cohort with different total cholesterol levels according to statin use.

	Statin group n = 173		Without statin group n = 365		
	< 5.4 mmol\L n = 143	5.4 – 7.2 mmol\L n = 29	< 5.4 mmol\L n= 155	5.4–7.2 mmol\L n = 184	> 7.2 mmol\L n = 26
Age, years, Me [IQR]	82.9 [81.2 – 85.7]	82.9 [81.8 – 85.6]	84.5 [82.7 – 87.3]	84.9 [81.4 – 86.9]	85.8 [82.5 – 86.9]
Male, n (%)	61 (42.7)	6 (20.7)	71 (45.8)	59 (32.1)	1 (3.8)
Education level, n (%)					
Without qualifications	1 (0,7)	–	1 (0,6)	2 (1.1)	–
Primary school	63 (44.1)	9 (31.0)	52 (33.8)	65 (35.5)	5 (19.2)
Lower secondary*	41 (28.7)	8 (27.6)	52 (33.8)	57 (31.1)	14 (53.8)*
Higher secondary	22 (15.4)	8 (27.6)	28 (18.2)	35 (19.1)	2 (7.7)
College	12 (8.4)	4 (13.8)	13 (8.4)	19 (10.4)	4 (15.4)
University	4 (2.8)	–	7 (4,5)	4 (2.2)	1 (3.8)
No information	–	–	1 (0,6)	1 (0,5)	–
Type of living status, n (%)					
Institutionalized	10 (7.0)	3 (10.3)	15 (9.7)	27 (14.8)	1 (3.8)
Alone at home	42 (29.4)	15 (51.7)	59 (38.1)	69 (37.7)	15 (57.7)
With partner at home	81 (56.6)	9 (31.0)	64 (41.3)	69 (37.7)	7 (26.9)
With children at home	10 (7.0)	2 (6,9)	15 (9.7)	17 (9.3)	3 (11.5)
Other	–	–	2 (1,3)	1 (0,5)	
Arterial hypertension, n (%)	116 (80.0)	20 (69.0)	109 (66.9)	122 (66.3)	17 (65.4)
Angina pectoris, n (%)	36 (25.2)	1 (3.4)	27 (17.5)	22 (12.0)	3 (11.5)
Myocardial infarction, n (%)	30 (21.0)	1 (3.4)	16 (10.3)	13 (7.1)	1 (3.8)
Atrial fibrillation, n (%)	25 (17.5)	4 (13.8)	32 (20.6)	42 (22.8)	3 (12.0)
Stroke, n (%)	17 (12.0)	3 (10.7)	13 (7.2)	12 (6.6)	–
Diabetes mellitus, n (%)	42 (29.0)	7 (24.1)	27 (17.4)	21 (11.4)	4 (15.4)
COPD, n (%)	21 (14.5)	2 (6.8)	23 (14.9)	25 (13.6)	3 (11.5)
Peripheral arterial disease, n (%)	20 (13.8)	2 (6,9)	12 (7.8)	14 (7,6)	–
Cancer:					
Active case, n (%)	17 (11.9)	2 (6,9)	12 (7.7)	10 (5.4)	–
Cured case, n (%)	14 (9.8)	4 (13.8)	22 (14.3)	23 (12.5)	4 (15.4)
Anaemia, n (%)*	37 (25.2)	8 (27.6)	42 (27.3)*	22 (12.0)	1 (3.8)
GDS ≥5, n (%)	19 (13.1)	9 (31.0)	30 (19.5)	49 (26.6)	4 (15.4)
SPPB < 8, n (%)	45 (32.6)	13 (46.4)	70 (46.7)	77 (44.0)	11 (42.3)
Index Barthel < 95, n (%)	110 (76.9)	23 (79.3)	115 (74.7)	143 (77.8)	18 (69.2)
MNA ≤ 23.5, n (%)	9 (6.2)	2 (6,9)	10 (13.7)	19 (23.8)	4 (33.3)
MMSE < 24, n (%)	21 (14.8)	2 (6,9)	27 (17.5)	34 (18.7)	4 (15.4)
TSG > 3.2 μU/ml, n (%)	6 (4,1)	1 (3.4)	5 (5.3)	19 (10.3)	3 (11.5)
hs-CRP > 0.3 mg/L, n (%)*	39 (27.9)	8 (27.6)	65 (42.8)*	55 (29.9)	9 (34.6)
BNP > 100 pg/ml, n (%)	8 (27.6)	68 (47.6)	84 (54.2)	86 (46.7)	10 (38.5)
GFR < 60 mL/min, n (%)*	13 (14.0)	2 (9,5)	10 (9,9)	15 (12.4)	6 (33.3)*

*p < 0.05.

Table 5
Assessment of mortality risk by the cholesterol levels in the BELFRAIL study.

	HR (95% CI)	HR (95% CI)	HR (95% CI)
5.4 – 7.2 mmol/L	1	1	1
< 5.4 mmol/L	**1.58 (1.04 – 2.41)**	1.94 (1.05 – 3.58)	1.82 (0.96 – 3.45)
> 7.2 mmol/L	1.53 (0.68 – 3.46)	1.41 (0.40 – 4.95)	1.45 (0.41 – 5.10)
Age	1.08 (1.02 – 1.12)	1.03 (0.96 – 1.12)	1.01 (0.93 – 1.10)
Sex	1.39 (0.91 – 2.15)	1.29 (0.69 – 2.41)	1.27 (0.68 – 2.39)
Educational levels	0.89 (0.75 – 1.07)	1.02 (0.79 – 1.32)	1.04 (0.80 – 1.35)
Current family situation	0.90 (0.71 – 1.15)	0.94 (0.68 – 1.30)	0.93 (0.67 – 1.29)
hs-CRP > 0.3		1.44 (0.80 – 2.59)	1.46 (0.81 – 2.62)
BNP < 100		1.65 (0.92 – 2.96)	1.62 (0.90 – 2.93)
MNA < 23.5		2.27 (1.20 – 4.28)	2.24 (1.17 – 4.28)
MMSE < 24		2,012 1,020 3.97)	2.05 (1.01 – 4.13)
Atrial fibrillation		1.30 (0.70 – 2.44)	1.39 (0.74 – 2.60)
Cancer		0.87 (0.59 – 1.30)	0.89 (0.60 – 1.33)
Anaemia			1.19 (0.63 – 2.27)

For total cholesterol levels < 5.4 mmol/L: Harrell's C (95% CI) - 0.56 (0.51 – 0.62).

independent mortality predictor in the elderly population after the exclusion of patients with acute diseases, dementia, infection, inflammation, malnutrition, cancer, and general health conditions of older adults (Cabrera et al., 2012).

We observed an association between low TC levels and atrial fibrillation that was consistent with the results of other studies (Li, Gao et al., 2018, 2018b; Liu et al., 2018; Watanabe et al., 2011). The specific mechanisms of this association remain unknown, although some hypotheses have been proposed (Annoura et al., 1999; Li, Gao et al., 2018; Liu et al., 2018). In addition, cholesterol modulates the distribution and function of some ion channels, including those of the Kv1.5 K + channel, Kir2.1 K + channel, and Na + channel, which may be involved in the pathogenesis of arterial fibrillation (Li, Gao et al., 2018). The observed association might partially explain the increased risk of mortality due to a higher incidence of cardio-embolic stroke (Tsuji, 2011).

The association between anaemia and low TC levels observed in our research was also found in other studies(Chowta, Chowta, Shet, Achappa, & Madi, 2017; Elmehdawi, 2008; Shirvani, Vakili Sadeghi, Hosseini, Bijani, & Ghadimi, 2017). Although the exact aetiology of low TC in anaemic patients is not known, some authors suggested that hypocholesterolaemia might be the cause of anaemia (Elmehdawi, 2008), while others suggested that anaemia could be the cause of a decreased TC levels (Elmehdawi, 2008). Furthermore, there is evidence that lipoprotein uptake pathways are affected by iron (Kohn, 1982). Anaemia and low TC were both found to be independent factors for all-cause mortality in older adults (Turusheva et al., 2015). Many common underlying conditions, such as chronic inflammation, chronic renal failure, nutrient deficiencies, hyperthyroidism, and adrenal failure, can lead to anaemia and low TC levels. Therefore, anaemia and low TC levels might just be symptoms of damage in several body systems (Kohn, 1982).

4.4. Implications of our results

Low TC may be an indicator of poor health status in older adults and should be taken into consideration in geriatric assessments. Further research on the causes of low TC in older adults and the specific mechanisms of the association between low TC and mortality is needed.

4.5. Strengths and limitations

There was no information about the precise causes of death in the Crystal study.

The strengths of this study are the prospective design, the comprehensive assessment of participants, the availability of the 2.5-year follow-up on mortality and no loss of mortality data for any participants. All participants were selected using a random sampling method. Internal and external validations were performed to assess the validity of the determined optimal cholesterol levels.

5. Conclusion

A U-shaped relationship between TC level and all-cause mortality was found. The TC range associated with the lowest mortality was 5.4–7.2 mmol/L. TC levels < 5.4 mmol/L were associated with a 3-fold increased risk of all-cause mortality, even after adjusting for age, sex and CVD. The association between low TC levels and a high risk of all-cause mortality was confirmed in a Belgian cohort of adults 80 years and older.

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Anna Turusheva, Elena Frolova, Bert Vaes, and Jean-Marie Degryse. The first draft of the manuscript was written by Anna Turusheva, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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