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Brief Communication

Reevaluating elevated HDL cholesterol levels in healthy older persons as a risk factor for various disease states

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Abstract: This article reviews the role of high-density lipoprotein cholesterol (HDL-C) in the elderly population, questioning the established view that advocates the ubiquitous health benefits of HDL cholesterol. High levels of HDL-C have been found to be associated with an increased risk of debilitating fractures, dementia, and cardiovascular disease, predominantly affecting older men, through the use of large population-based studies such as the ASPREE trial and the UK Biobank. Possible mechanisms are closely linked to cholesterol crystallization and altered HDL particle function. These findings call for a refinement of the understanding of high-density lipoprotein cholesterol (HDL-C), which implies adjustments to clinical guidelines and risk assessment strategies in older populations.

Keywords: High-density lipoprotein cholesterol (HDL-C), elevated levels, risk factor, older persons, disease

Elevated HDL-C (high-density lipoprotein cholesterol), traditionally viewed as cardioprotective and indicative of good health, is now under scrutiny. Recent research challenges this notion, suggesting that abnormally high HDL-C levels might paradoxically increase disease susceptibility in various organ systems. For instance, studies have indicated potential links between high HDL-C levels and increased risks of fracture [1], neurological conditions [2], and certain cardiovascular diseases [3], necessitating a reevaluation of its role in overall health.

A few recent studies challenge the traditional oversimplified view that HDL cholesterol is a clear sign of good health [1, 2]. In these large community-based cohort studies by The Aspirin in Reducing Events in the Elderly (ASPREE) trial and UK Biobank, researchers observed that among older adult males, very high levels of HDL-C were unexpectedly linked to increased risks of fragility fractures, non-cancer/non-cardiovascular mortality, and all-cause mortality. This association persisted even after adjusting for atherosclerotic disease and lipid-lowering medication usage. Concurrent studies highlight the complex effects of elevated HDL-C, such as its links to sepsis, vision impairment, immunological issues, and cognitive decline. Potential mechanisms for these unexpected outcomes include impaired reverse cholesterol transport, antioxidant dysfunction, vascular homeostasis disturbance, complement system activation, and cholesterol crystallization in delicate tissues. These findings necessitate further research to unravel the complex phenotypes associated with abnormally high HDL-C levels, particularly in various subpopulations. This emerging evidence suggests a more nuanced interpretation and calls for a reevaluation of the 'ideal' HDL-C range.

In detail, recent studies have begun to explore the complex relationship between HDL cholesterol and bone health, particularly in older adults. In a significant longitudinal study involving 16,262 older adults [1], it was found that higher HDL-C levels correlated with an increased risk of fractures. Over a median follow-up of 1.4 years, participants with higher HDL-C had a 14% increase in fracture risk for each standard deviation increase in HDL-C, even after full adjustment for other risk factors. These findings suggest that the relationship between

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HDL-C and bone health is not straightforward. Dr. Hussain notes the unique association of high HDL-C levels with increased fracture rates, independent of other risk factors. This challenges existing fracture prevention guidelines, which do not currently consider high HDL-C levels. These results underscore the need for a more comprehensive risk assessment of bone health, factoring in HDL-C levels. It highlights the dual nature of HDL-C, beneficial at moderate levels but potentially detrimental at higher concentrations, thus questioning the traditional perception of HDL-C as an unambiguous marker of good health.

And the relationship between high HDL-C levels and cognitive health has been explored in recent studies, particularly in the elderly. The ASPREE study by Monash University researchers [2], examining over 18,600 healthy individuals aged 70 and above, found that those with very high HDL-C levels (>80 mg/dL) had a notably increased risk of dementia. This risk was more pronounced in seniors aged 75 and above. These findings highlight that the risk associated with high HDL-C is not confined to cardiovascular health alone. Dr. Monira Hussain, the lead author, suggests that functional changes in HDL particles at high concentrations might be driving this increased risk of cognitive decline. This study underscores the complexity of HDL-C's role in health, challenging the notion that high levels are universally beneficial. It suggests the need for further research to understand the implications of very high HDL-C levels on brain health, especially in older populations.

While HDL cholesterol is traditionally associated with cardiovascular benefits, recent studies have begun to question this simplistic view. A 2022 study involving 11,987 individuals with hypertension discovered a J-shaped relationship between HDL-C levels and cardiovascular events [3]. Both low and high HDL-C levels were linked to increased risk compared to moderate levels, with this phenomenon being more pronounced in males, possibly influenced by endogenous estrogen. Both low and high HDL-C levels were linked to increased risk compared to moderate levels, with this phenomenon being more pronounced in males, possibly influenced by endogenous estrogen. Dr. Gaetano Santulli highlighted a key finding from this study: a linear correlation between HDL-C levels and ryanodine receptor glycation, suggesting a potential underlying disease mechanism. These findings point to the need for a reassessment of HDL-C's role in health, especially the implications of very high levels. They suggest that abnormally high HDL-C could indicate dysfunction and increased risk, necessitating a revision of risk assessment algorithms and lipoprotein ranges.

A study produced insightful results regarding gender-based differences in results. This study looked into the relationship between death rates and baseline HDL-C levels in older, initially healthy men and women. A matched cohort from the UK Biobank (UKB; n=62,849 aged ≥65 years) and participants from the Aspirin in Reducing Events in the Elderly (ASPREE; n=18,668) trial were included in the analysis. During a mean follow-up of 6.3±1.8 years, 1836 deaths occurred among ASPREE participants (mean age 75±5 years). Highest category HDL-C levels in men were linked to higher risks of cancer (HR 1.37, 95% CI 0.96-2.00), all-cause (HR 1.60, 95% CI 1.26-2.03), and "non-cancer non-CVD" (HR 2.35, 95% CI 1.41-3.42) death, but not of CVD (HR 1.08, 95% CI 0.60-1.94). Replicating these relationships were UKB participants (mean age 66.9±1.5 years) who had an average follow-up of 12.7±0.8 years and 8739 deaths. The relationship between female death rates and HDL-C levels was not determined to be significant. In healthy older males, higher HDL-C levels were associated with a higher risk of cancer and "non-cancer non-CVD" death, while this association was not seen in women [4].

In conclusion, whereas moderate HDL cholesterol levels are linked to positive cardiometabolic profiles, new research challenges the notion that extremely high concentrations of the protein are inherently healthy. Large observational studies show that, despite common risk factors, older persons with HDL cholesterol levels over 80 mg/dL paradoxically had increased risks of death, cancer, dementia, fractures, and cardiovascular events. Theoretical explanations for these changes in function include immunological activation, tissue cholesterol crystallization, vascular homeostasis abnormalities, and disrupted reverse cholesterol transport capacities. Notably, post-trans-

lational modification of proteins is closely linked to HDL dysfunction and plays a crucial role in regulating organ health. These findings demand that risk assessment for each individual go beyond the simple "good cholesterol/bad cholesterol" dichotomy. Additionally, they call for a reassessment of the typical physiological ranges used in prediction algorithms and clinical guidelines. Although ordinary levels of HDL cholesterol seem beneficial, excessively high values may indicate dysfunctionality and increase vulnerability to many morbid occurrences, therefore more basic, translational, and clinical research is necessary.

Disclosure of conflict of interest

None.

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