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Renal Dysfunction and Low HDL Cholesterol in Indian Elderly

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ABSTRACT

Objective: The elderly has a significant morbidity and mortality rate from chronic kidney disease (CKD) and cardiovascular disease (CVD). In CKD patients, low levels of high-density lipoprotein cholesterol (HDL-C), a conventional CVD risk factor, are prevalent. In the community-dwelling population, nothing is known regarding the link between low HDL-C and renal impairment.

Methods: This was a population-based cross-sectional study with 4,753 people participated, which was a retrospective study. The Modification of Diet in Renal Disease (MDRD equation) equation was used to compute the estimated glomerular filtration rate (eGFR). Multiple logistic regression models and restricted cubic splines were used to investigate the links between renal impairment and low HDL-C.

Results: 620 (13.34 percent) of the 4,649 people who fit the criterion had low HDL-C levels of less than 40 mg/dl. Lower eGFR of 60 to 90 ml/min/1.73 m2 (OR, 2.03; 95 percent CI, 1.21–3.43) and marginal eGFR of 60 to 90 ml/min/1.73 m2 (OR, 1.26; 95 percent CI, 1.01–1.58) were significantly associated with low HDL-C in the fully adjusted model, compared to normal eGFR of 90 ml/min/1.73 m2. Furthermore, secondary studies employing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation yielded consistent results. A substantial dose-response connection between eGFR and low HDL-C was found using fully adjusted cubic spline models (P for non-linearity, 0.356).

Conclusion: Renal dysfunction was independently and strongly linked with low HDL-C in this general senior population, and the incidence of low HDL-C increased with decreasing eGFR, suggesting that even minor changes in renal function may be associated with changed lipid levels.

Keywords: renaldys function, dyslipidemia, estimated glomerular filtrationrate, high-density lipoprotein cholesterol, cardiovascular prevention

INTRODUCTION

Over the last two decades, India has made amazing progress in reducing the burden of cardiovascular disease (CVD), with the standardised death rate dropping significantly (1). In patients with chronic kidney disease (CKD), however, the disease burden caused by CVD remains substantial (2). According to the yearly report of the India Kidney Disease Network

(IK-NET), the prevalence of CVD in CKD patients in India is as high as 50.8 percent (3). CVD is the major cause of death in CKD patients at all stages of the disease (4), particularly in patients with end-stage renal disease (ESRD), where the CVD mortality rate is 10– 20 times that of the general population (5).Population aging, on the other hand, is increasing as a result of socioeconomic progress. India is expected to have 300 million individuals aged 60 and up by 2025, according to estimates (6). According to studies, the illness load increases with age in CKD patients (7, 8), and nearly half of CKD patients were 60 years or older (3). As a result, preventing CVD events in the aged population, particularly those with CKD, is critical.

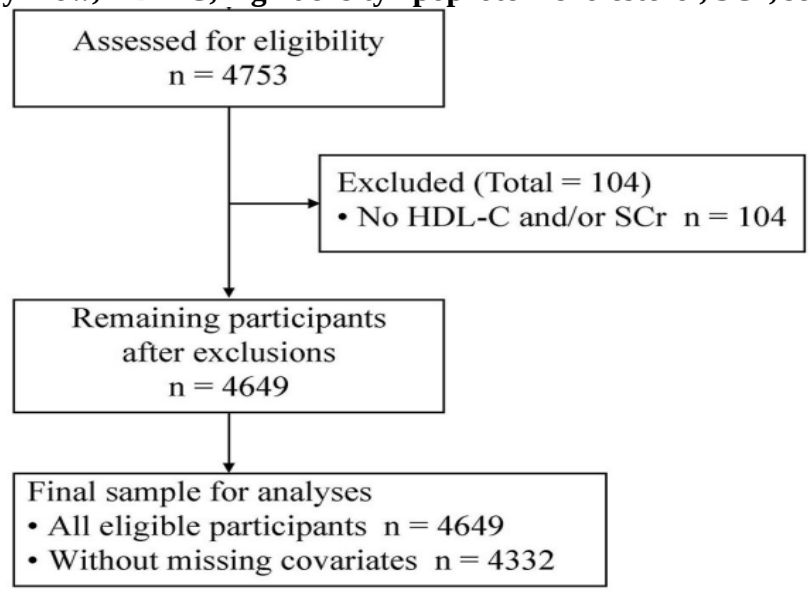
HDL-C (high-density lipoprotein cholesterol) is a classic CVD preventive factor (9), which was assumed to work by modulating the reverse cholesterol transport pathway (10, 11), but it has been shown to drop dramatically in CKD patients (12, 13). According to the Framingham Heart Study, an increase in HDL-C of 1 mg/dl (0.026 mmol/L) lowered CVD risk by 2–3 percent (14). Since then, a growing number of epidemiological studies have confirmed and built on the findings (15). Previous research has found a link between HDL-C and renal function in adults (16–19). However, the link between low HDL-C and renal impairment has yet to be shown, particularly in Indian old people living in the community.Because changes in HDL-C may be related to age, gender, body weight, physical activity, medication, disease, and other factors (20), the independent association between HDL-C and renal dysfunction in the community elderly population should be estimated after these potential confounders have been taken into account.

METHODS

StudyPopulation

Since 2013, this study has been a multistage cluster sample survey of community non-institutionalized residents aged 60 and older. The specifics of its design have already been discussed (21). In a nutshell, 4,753 community members aged 60 to 104 years old were recruited in 2017 and underwent a full health assessment. After fasting for at least 10 hours overnight, participants had blood tests, and blood samples were transferred to the Blood Laboratory, which is connected, for measurement within 2 hours.Inthecurrentanalysis,104participantswereexcludedduetomissingbothHDL-Candserumcreatinine(SCr)measurements,so4,649participantswereincluded(**Figure1**).

Figure 1: Study Flow, HDL-C, high density lipoprotein cholesterol, SCr, serum creatinine



DATA COLLECTION

Participants' demographics, habits, medication and disease histories, and other details were

gathered using standardised questionnaires. It was recorded if postmenopausal women were using oestrogen and/or progestin as hormone replacement therapy.

The BMI was computed by dividing the weight in kilos by the height in metres squared. A waist circumference of >90 cm in men and >80 cm in women was considered as abdominal obesity (22). The Cockcroft-Gault equation was used to calculate creatinine clearance (CCr) (23). Smoking more than 100 cigarettes in a lifetime and still smoking was considered as current smoking. Current drinking is defined as consuming one or more alcoholic beverages per week in the preceding year. Physical activity was defined as more than 30 minutes per day of exercise or recreational activities on at least four days per week.

Hypertension was defined as an average of two measures of systolic blood pressure of 140 mmHg or diastolic blood pressure of 90 mmHg, or normal blood with concomitant use of antihypertensive medications, or normal blood with concomitant use of antihypertensive agents (24). Diabetes was defined as fasting plasma glucose of less than 7.0 mmol/L or current insulin or oral anti-diabetic medication use. A history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic event, or atherosclerotic peripheral artery disease was characterised as atherosclerotic cardiovascular disease (ASCVD) (25). Aspartate aminotransferase >40 U/L, alanine aminotransferase >50 U/L, or a history of liver disease were used to define liver dysfunction. The outpatient medical records of primary care in community health centres were used to corroborate all disease histories.

Table1|Baseline characteristics of participants according to low HDL-C status

Characteristics	**All (*n* =4,649)**	**Low HDL-C**		***P*-value**
		Yes(*n*=620)	No(*n*=4,029)	
Age(Years)	72(6)	72(6)	72(6)	0.560
Male	2,090(44.96)	371(59.84)	1,719(42.67)	<0.001
BMI(kg/m^2)	24.68(3.46)	25.68(3.03)	24.52(3.50)	<0.001
WC(cm)	87.84(12.22)	90.94(10.71)	87.37(12.37)	<0.001
Abdominalobesity	2,527(54.36)	369(59.52)	2,158(53.56)	0.001
Currentsmoking	971(20.89)	174(28.06)	797(19.78)	<0.001
Current drinking	747(16.07)	115(18.55)	632(15.69)	0.071
Physicalactivity	3,902(83.93)	519(83.71)	3,383(83.97)	0.871
Statin	377(8.11)	57(9.19)	320(7.94)	0.335
β-Blocker	281(6.04)	47(7.58)	234(5.81)	0.105
Hormones	21(0.45)	4(0.65)	17(0.42)	0.653
ASCVD	728(15.66)	117(18.87)	611(15.17)	0.018
Diabetes	1,640(35.28)	277(44.68)	1,363(33.83)	<0.001
Hypertension	3,454(74.30)	496(80.00)	2,958(73.42)	<0.001
Liverdysfunction	224(4.82)	43(6.94)	181(4.49)	0.008
Homocysteine(μmol/L)	14.90(12.60–18.00)	16.30(13.70–19.78)	14.60(12.50–17.70)	<0.001
SBP(mmHg)	141.98(20.72)	142.77(19.65)	141.85(20.88)	0.298
DBP(mmHg)	80.45(10.75)	80.63(10.65)	80.44(10.70)	0.685
HbAIc(%)	6.00(5.80–6.50)	6.20(5.80–6.80)	6.00(5.80–6.40)	<0.001
FPG(mmol/L)	5.38(4.94–6.24)	5.65(5.07–6.96)	5.36(4.93–6.14)	<0.001
TC(mg/dl)	192(48)	171(35)	195(49)	<0.001
TG(mg/dl)	124(91–172)	195(141–274)	118(88–159)	<0.001
LDL-C(mg/dl)	127(37)	112(32)	129(37)	<0.001
ALT(U/L)	16(12–21)	18(13–24)	15(12–21)	<0.001
AST(U/L)	20(18–24)	20(17–24)	20(18–24)	0.049
UN (mg/dl)	15.78(4.41)	15.78(4.81)	15.78(4.35)	0.977

UA(mg/dl)	5.63(1.46)	6.17(1.55)	5.54(1.43)	<0.001
SCr(mg/dl)	0.87(0.25)	0.93(0.29)	0.86(0.24)	<0.001
CCr(ml/min)	66.47(18.76)	68.70(18.12)	66.13(18.84)	0.002
eGFR(MDRD)(ml/min/1.73m^2)				0.001
60<	126(2.71)	25(4.03)	101(2.51)	
60–90	1,198(25.77)	189(30.48)	1,009(25.04)	
≥90	3,273(70.40)	400(64.52)	2,873(71.31)	
eGFR(CKD-EPI)(ml/min/1.73m^2)				<0.001
60<	570(12.26)	105(16.94)	465(11.54)	
60–90	3,087(66.40)	401(64.68)	2,686(66.67)	
≥90	940(20.22)	108(17.42)	832(20.65)	

Data are mean (standard deviation), median (interquartile range), or frequency (percentage). Hormones refers to hormone replacement therapy for postmenopausal females as estrogenand/ orprogestin.

HDL-C,high-density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; ASCVD, athero sclerotic cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbAIc, hemoglobin AIc; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; ALT, alanine amino transferase; AST, as part ate amino transferase; UN, urea nitrogen; UA, uric acid; SCr, serum creatinine; CCr, creatinine clearance; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

OUTCOME ASCER TAINMENT

In this study, estimated glomerular filtration rate (eGFR) was used to assess renal dysfunction. eGFR was calculated using the Modification of Diet in Renal Disease(MDRD) equation where eGFR (ml/min/1.73 m^2) = 186 ∗SCr(mg/dl) $^{-1.154}$∗ age (years)$^{-0.203}$∗ 0.742 (if female) ∗ 1.233 (if Indian) (26) [with subsidiary analyses using eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (27)].

STATISTICAL ANALYSES

Low HDL-C was the study's endpoint, which was defined as less than 40 mg/dl according to Indian recommendations (28). For continuous variables, the mean [standard deviation (SD)] or median [interquartile range (IQR)] were used, and for categorical variables, the frequency (%) was used.

Student's t-test, Welch's t-test, and Mann–Whitney U test for normally or skewed distributed continuous variables, and Chi-square test for categorical variables were used to determine statistical significance. The association between HDL-C and renal function was first assessed using Pearson's correlation coefficients.

The connection between eGFR and low HDL-C was studied using multiple logistic regression models. Three different models were used: Model I is unadjusted; Model II is adjusted for age, gender, and BMI; and Model III is adjusted for smoking, drinking, physical activity, -blocker, statin, diabetes, liver dysfunction, ASCVD, and triglycerides, as well as other factors. To mimic the relationship between eGFR and low HDL-C, restricted cubic splines with three knots at the 25th, 50th, and 75th percentiles were used.

All *P*-values were two-sided, and statistical significance was defined as $P<0.05$. Analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

BASELINE CHARACTERISTICS

2,090 (44.96 percent) of the 4,649 participants were men, 1,640 (35.28 percent) had diabetes,

and 224 (4.82 percent) had liver disease. The mean (SD) age was 72 (6) years; the mean (SD) eGFR for the MDRD and CKD-EPI equations was 101.77 (22.56) and 77.27 (14.35) ml/min/1.73 m^2, respectively; and the mean (SD) HDL-C was 55 (16) mg/dl. In 620 subjects, low HDL-C was found (13.34 percent). Participants with low HDL-C were more likely to be males, obese, current smokers, hypertensive, diabetic, and ASCVD patients than those with normal HDL-C. (Table 1).

HDL-C AND RENAL FUNCTION

Table 2 shows the results of a preliminary investigation into HDL-C and renal function. UN, UN/SCr, and eGFR were favourably connected with HDL-C, while UA, SCr, and CCr were negatively correlated (P 0.010). Despite the fact that there were substantial connections between HDL-C and renal function, they were all weak. As a result, more research was done.

Table 2: Pearson's correlation coefficients between HDL-C and renal function

	HDL-C		
	r	**95% CI**	**P-value**
UA	-0.261	-0.289 ~ -0.236	<0.001
UN	0.038	0.010 ~0.069	0.010
SCr	-0.140	-0.167 ~-0.114	<0.001
UN/SCr	0.173	0.143 ~0.203	<0.001
CCr	-0.153	-0.181 ~-0.122	<0.001
eGFR, MDRD	0.047	0.017 ~0.080	0.002
eGFR, CKD-EPI	0.048	0.017 ~0.079	0.001

UN, urea nitrogen, UA, uric acid, serum creatinine, BMI, body mass index, ASCVD, atherosclerotic cardiovascular disease, CCr, creatinine clearance, eGFR, estimated glomerular filtration rate, MDRD, Modification of diet in renal disease, CKD-EPI, chronic kidney disease epidemiology collaboration, CI, confidence interval eGFR and Low HDL-C

Decreased eGFR (MDRD) showed a significant independent association with low HDL-C. Compared with normal eGFR, the unadjusted odds ratios (OR) for lower and marginal eGFR were 1.78 (95% CI, 1.13–2.79) and 1.35 (95% CI, 1.12–1.62), respectively (Model I). The association was further strengthened, and the ORs were 1.81 (95% CI, 1.13–2.90) and 1.33 (95% CI, 1.10–1.62), respectively, after adjustment for age, gender, and BMI only (Model II). After adjusting for lifestyles, medication and disease history, and triglycerides, the link with low HDL-C was substantially larger in lower (OR, 2.03; 95 percent CI, 1.21–3.43) and marginal eGFR (OR, 1.26; 95 percent CI, 1.01–1.58). (Model III). eGFR was shown to be substantially linked with low HDL-C (unadjusted OR (95 percent CI) per SD decrease: 1.15 (1.05, 1.25), P= 0.002; multivariable-adjusted OR (95 percent CI): 1.16 (1.06, 1.27), P = 0.001; in Model III: 1.17 (1.06, 1.30), P= 0.002). (Figure 2). A restricted cubic spline model was fitted to see if the link between eGFR and low HDL-C was linear, and no indication of non-linearity was detected (P for non-linearity, 0.356).

SUBSIDIARY ANALYSES

To double-check the findings, the CKD-EPI equation was utilised to calculate eGFR instead of theMDRD equation (27). The results showed that low HDL-C was associated with lower eGFR in any of the models, and the ORs were increased after adjusting for lipid metabolism confounders (OR (95 percent CI): in Model I: 1.74 (1.30, 2.33), P< 0.001; in Model II: 2.05 (1.46, 2.88), P< 0.001; in Model III: 2.05 (1.44, 2.92), P< 0.001).In any of the models, however, the link of low HDL-C with marginal eGFR was not statistically significant when compared to normal eGFR (all P > 0.1). Notably, the degree of association and non-linear relationship between low HDL-C and eGFR, as a continuous variable, remained relatively consistent [completely adjusted OR (95 percent CI), 1.17 (1.06, 1.29); P for non-linearity, 0.602].

DISCUSSION

Age, gender, BMI, smoking, drinking, physical activity, β-blocker, statin, diabetes, liver dysfunction, ASCVD, and triglycerides were shown to be substantially linked with low HDL-C in community-dwelling elderly, and this connection was independent of identified HDL-C confounders. The findings also back up some of the prior findings from population studies: Males had lower HDL-C levels than females (29, 30), HDL-C levels dropped with rising BMI and triglycerides (31, 32), and HDL-C levels were greater in people who drank alcohol (33, 34).

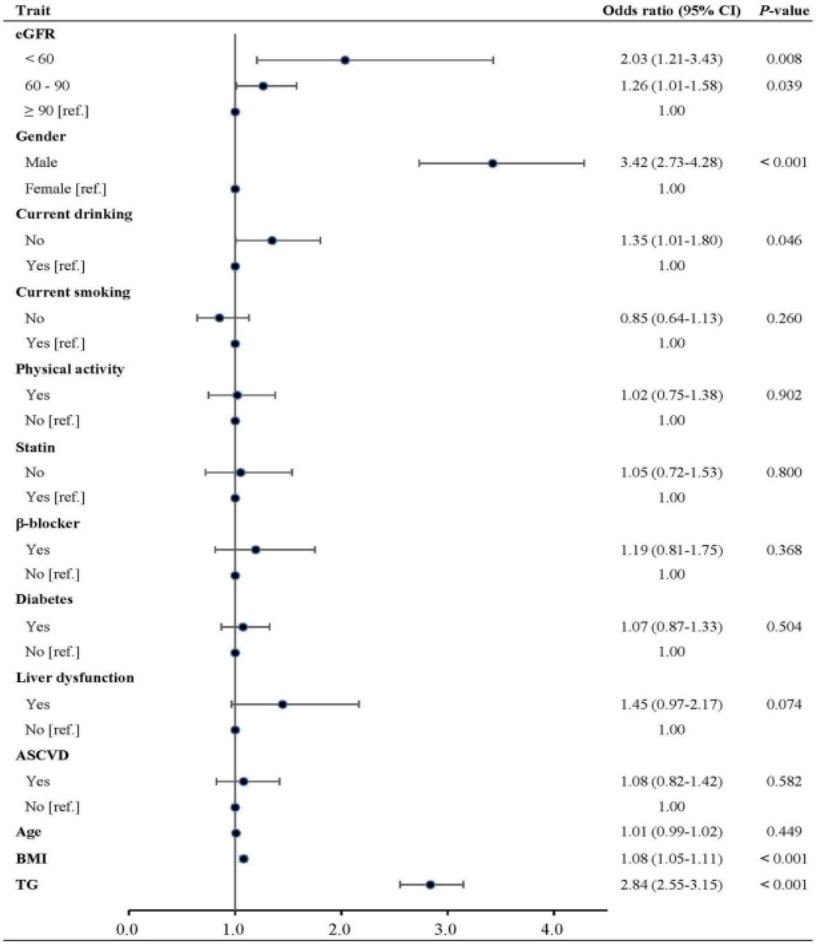
Low HDL-C is hypothesised to be linked to a drop in eGFR, which could be linked to major alterations in proteomics and lipidomics. ApoA-I levels were observed to be considerably lower in ESRD patients, owing to both defective synthesis and increased catabolism of ApoA-I in CKD patients, according to Vaziri et al. ApoA-I is an important component of HDL particles, and as CKD progresses, its concentration drops, resulting in a drop in HDL-C. (35). Meanwhile, in CKD patients, the loss of hepatic triacylglycerol lipase causes a drop in HDL cholesterol and an increase in triacylglycerol (36).In CKD patients, however, oxidative stress and inflammatory reactions, as well as uremic toxins, cause denaturation, oxidation, and carbamylation of ApoA-I and other protein components of HDL particles, affecting HDL's binding to cell surface cholesterol transporters and lowering HDL's ability to promote cholesterol efflux (37, 38). This inhibits reverse cholesterol transfer, promoting foam cell formation, accelerated atherosclerosis, endothelial dysfunction, oxidative stress, systemic inflammation, and glomerulosclerosis, all of which increase the onset and progression of CVD or ESRD (12). As a result, it's reasonable to assume that a low HDL-C level is linked to a lower eGFR.

Low HDL- C, on the other hand, has been linked to a decline in renal function in earlier investigations (16–19). The MDRD study (16) found that low HDL-C could predict an increase in renal dysfunction in 840 patients with various kidney illnesses, which was consistent with the results of the Atherosclerosis Risk in Communities (ARIC) cohort study (17). Bowe et al. conducted a retrospective cohort study of approximately 2 million male veterans using VA databases and discovered that low HDL-C was substantially related with the probability of acute renal disease and progression (18).Meanwhile, low HDL-C has been suggested as a proxy measure for poor overall metabolic health (18). Our data imply that lower eGFR, even in the general population, may lead to poor overall metabolic health and thus indirectly increase CVD risk. Lees et al. included eGFR into a classic CVD risk prediction model and found that it considerably improved the models' risk prediction capacity (39), which is similar to the findings of the current investigation. Furthermore, data from the UK Biobank revealed that simply looking at total cholesterol and HDL-C might predict the effect of blood lipids on CVD risk (40).Since a result, HDL-C levels should be monitored more closely in the general population, particularly in individuals with renal dysfunction, as they may help forecast the onset of CVD as early as feasible.

The results of the analysis employing the MDRD and CKD-EPI equations for the connection of low HDL-C with marginal eGFR were different, which could be due to discrepancies in the original populations used to generate the equations. The MDRD equation was developed using CKD patients, and the connection between GFR and SCr concentrations differs between healthy and CKD people (41). As a result, it's unsurprising that the MDRD equation consistently underestimates GFR at high GFR values (>60 ml/min/1.73 m2). Because of this systematic underestimating at the population level, the prevalence of CKD stage III (eGFR 60 ml/min/1.73 m2) in the general population is overestimated.The population utilised to build the CKD-EPI equation, on the other hand, was largely those with GFR > 60 ml/min/1.73 m^2, which helped to correct the MDRD equation's bias (27). As a result, the CKD-EPI equation performed

better for people with GFR >60 ml/min/1.73 m^2, which was also observed in the European geriatric population (42). However, as compared to the MDRD equation, the CKD-EPI equation only exhibited a modest improvement in precision (43, 44).Murataetal.comparedtheaccuracyoftheMDRD and CKD-EPI creatinine equations for estimating GFR in 5,238patients and confirmed that the CKD-EPI creatinine equationunderestimatedGFRtoalesserextentthantheMDRDequationin pre- and post-donation kidney donors. The CKD-EPI equation, on the other hand, did not perform better or even slightly worse than the MDRD equation in patients with native CKD, renal transplant recipients, and other organ recipients, with a tendency to overestimation (45). This overestimation in patients with CKD could be the cost of better performance at higher GFR levels (44, 46). Furthermore, van den Brand et al. studied 6,097 Caucasian participants and estimated eGFR using the MDRD and CKD-EPI equations, finding that the CKD-EPI had greater estimations of GFR for subjects under 70 years, but lower values for those 70 years and older (47). As a result, it's possible that the MDRD and CKD-EPI equations complement each other in terms of epidemiological study validation.

Figure 2: Multivariate-adjusted odds ratios of low HDL-C in participant subgroups, HDL-C, high-density lipoprotein cholesterol, eGFR, estimated glomerular filtration rate, BMI, body mass index, ASCVD, atherosclerotic cardiovascular disease, TG, triglycerides



A large natural population of elderly adults, various confounders, medical record analysis to determine illness status, and adoption of the India -specific eGFR criteria were all highlights of this study. All of these factors contribute to the reduction of prejudice.

It's important to recognise the study's limitations. To begin with, due to the nature of cross-sectional studies, it is unclear whether the relationship between eGFR and low HDL-C changes over time, making causality between the two impossible to establish. Second, while factors

impacting HDL-C levels have been taken into account to the greatest extent feasible, unmeasured confounders may still exist. Finally, all of the participants were older Indian individuals, making it impossible to generalise to other ethnic groups. Furthermore, according to the MDRD equation, over 70% of the participants in this group had normal renal function, which was much greater than the senior Caucasian population (48).Despite the fact that earlier studies have shown that Asians have a lower prevalence of CKD than Caucasians after correcting for sex and age (49), given that GFR decreases with age, the idea that this is an artefact of the MDRD equation cannot be ruled out. Finally, numerous assessments of renal functional state were not possible due to the nature of epidemiological investigations. In community populations, low eGFR may indicate an episode of acute renal damage, but this is less likely. Regardless of the equations used, there are limitations to estimating GFR in older persons, but these equations are all commonly utilised in the clinical context, thus knowing the relationship between eGFR and lipids remains crucial.It's also comforting to know that, despite these limitations, renal failure and low HDL-C had similar degree of association and dose-response associations, regardless of the methodologies employed to define renal dysfunction.

CONCLUSION

Renal impairment was highly linked to low HDL-C in this older cohort, even after controlling for known HDL-C variables. Low HDL-C and eGFR had a dose-response relationship, with the incidence of low HDL-C increasing as eGFR decreased. These findings highlight the potential that even minor alterations in renal function in humans are linked to lipid levels. As a result, it's possible that renal impairment and lipid alterations are causally linked, which should be investigated further in prospective investigations.

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