Serum cholesterol, both total and lipoprotein fractions, has been associated with mid- and late-life depression. Using longitudinal data on a large and ethnically diverse sample of urban adults, the associations of serum lipid profile measured by high or low total cholesterol (TC; > 200 mg dl⁻¹; < 160 mg dl⁻¹) and by atherogenic indices, namely high total cholesterol and low-density lipoprotein cholesterol relative to high-density lipoprotein cholesterol, with change in total and domain-specific depressive symptoms over time were examined. Findings were compared by sex. (Hypothesis 1) In addition, baseline depressive symptoms as predictors for longitudinal change in lipid profile trajectory were tested. (Hypothesis 2) Mixed-effects regression analyses stratified by sex was used. Sample sizes of participants (n) and repeated observations (n’) were: Hypothesis 1 (Men: n = 826 ; n’ = 1319; Women: n = 1099 ; n’ = 1817); Hypothesis 2 (Men: n = 738; n’ = 1230; Women: n = 964; n’ = 1678). As hypothesized, a higher level of atherogenic indices was linked to faster increase in depressive symptom scores, particularly depressed affect and interpersonal problems, though this relationship was found only among women. Among men a U-shaped relationship between baseline TC and longitudinal increase in somatic complaints and a direct link between low TC and longitudinal putative improvement in positive affect was found. On excluding statin users among women, low TC was associated with slower increase in depressed affect over time, whereas high TC was associated with faster increase in interpersonal problems. In summary, atherogenic indices were directly linked to faster increase in depressive symptoms among women only. More studies are needed to explain these sex-specific associations.
MATERIALS AND METHODS

Database and study sample

The HANDLS study is an ongoing prospective cohort study. Initiated in 2004, HANDLS recruited a representative sample of African Americans and whites (30–64 years old) living in Baltimore, MD, USA. Using an area probability sampling design of 13 neighborhoods (groups of contiguous census tracts), phase 1 consisted of screening, recruitment and household interview, whereas phase 2 consisted of examinations in mobile Medical Research Vehicles. Written informed consent was obtained from all the participants following their access to a protocol booklet in layman’s terms and a video describing all procedures and future re-contacts. Materials’ approval was obtained from the MedStar Institutional Review Board. We use longitudinal data from baseline and the first follow-up examination (visit 2 ended in 2013). Time between visits 1 and 2 ranged from <1 year to ~8 years, with a mean ± SD of 4.65 ± 0.93 years. Initially, 3720 participants were recruited (Sample 1), of whom 2177 (58.5%) had complete baseline phase 2 examination and non-missing dietary data (Sample 2, 2 days of dietary recall). Of those, all participants had non-missing data on depressive symptoms (Sample 3, n = 2177). This study restricted data to participants with 2 days of dietary recall and CES-D data at visits 1 or 2 or both (n = 2053; Sample 4). Out of Sample 4, we restricted our sample further to those with complete data on baseline serum cholesterol, HDL-C and LDL-C, and on CES-D (Sample 5A, n = 1925; 826 men and 1099 women). Repeated observations for Hypothesis 1 were n = 3136 (1319 in men and 1817 in women). Participants selected into Sample 5A, compared with the remaining HANDLS participants in Sample 1, had a lower percentage with Poverty Index Ratio (PIR) >125% (57 vs 61%, P = 0.011), and a higher percentage of women (57 vs 52%, P = 0.003) though no significant differences were found in age and race distributions.

In addition, for Hypothesis 2, the final sample size consisted of participants with complete lipid profile variables at visits 1, 2 or both and had complete data on CES-D total score at visit 1 (Sample 5B, n = 1702; 738 men and 964 women), with similar selectivity patterns as for Sample 5A. Repeated observations for Hypothesis 2 were n = 2908 (1230 in men and 1678 in women).

Depressive symptoms

Depressive symptoms were measured using the CES-D scale, at both baseline and follow-up HANDLS visits. The CES-D is a 20-item self-report symptom rating scale that assesses affective and depressed mood. A score ≥16 on the CES-D is a commonly used indicator for elevated depressive symptoms (EDS), associated with clinical depression based on the diagnostic and statistical manual, fourth edition criteria. Four CES-D subscales were derived and shown to have an invariant factor structure across visits and race distributions.

In addition, for Hypothesis 2, the final sample size consisted of participants with complete lipid profile variables at visits 1, 2 or both and had complete data on CES-D total score at visit 1 (Sample 5B, n = 1702; 738 men and 964 women), with similar selectivity patterns as for Sample 5A. Repeated observations for Hypothesis 2 were n = 2908 (1230 in men and 1678 in women).

Serum cholesterol and atherogenic indices

TC, HDL-C and TA (triaclyglycerols) were assessed using a spectrophotometer (Olympus 5400, Olympus, Melville, NY, USA). LDL-C was calculated as TC – (HDL-C+TA/5) and directly measured in a subsample (N = 236) also using a spectrophotometer (Olympus 5400). The correlation between those with baseline calculated LDL-C and those with measured LDL-C was r = 0.95. From these measures, two relative measures were obtained, namely TCHDL-C and LDL-CHDL-C ratios. Those two relative measures, also termed ‘atherogenic indices’ were previously studied in relation to various cardiovascular outcomes and were found to be positively associated with measures of atherosclerosis and coronary heart disease. Moreover, TC, categorized as low (< 160 mg dl⁻¹), medium (160–200 mg dl⁻¹) and high (> 200 mg dl⁻¹) was considered as a third major exposure in the analysis predicting depressive symptoms from serum lipid levels.

Covariates

Socio-demographic, lifestyle and health-related potential confounders. Some covariates were considered potential confounders: age, sex, race (white vs African American), marital status (married vs unmarried), completed years of education (0 ≤ High School; 1 = High School and 2 ≥ High School), poverty income ratio (0 = PIR < 125%; 1 = PIR ≥ 125%), measured body mass index (kg/m²), current use of drugs (opiates, marijuana or cocaine = 1 vs not = 0), and current smoking status (0: ‘never or former smoker’ and 1 ‘current smoker’). Finally, ‘statin use’ vs not at baseline was used as an indicator variable to conduct a sensitivity analysis among non-users as well as to control for statin use in the models. This was done given the known relationship between statin use and serum lipid change over time as well as statin use and baseline elevated serum TC.

Dietary potential confounders. Potentially confounding nutrients (per 1000 kcal) formerly linked to depression were: vitamins B-6, folate and B-12, total carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lutein + zeaxanthin, lycopene), vitamin C and α-tocopherol and the ratio of n-3 PUFA:n-6 PUFA. To emulate a multivariate nutrient density model, total energy intake was included as a covariate in the following paper, overall dietary quality was measured by the Healthy Eating Index (HEI-2010). A similar index was also included. The National Cancer Institute’s Applied Research website provided steps for calculating HEI-2010 component and total scores (http://appliedresearch.cancer.gov/tools/hei/tools.html). Detailed description of the procedure used is available on the HANDLS website (http://handls.nih.gov/O6Coll-dataDoc.htm). Total and component HEI-2010 scores were calculated for each recall day (day 1 and day 2) and then averaged to obtain the mean HEI-2010 total and component scores for both days combined. In the present study, only total HEI-2010 score was considered.

Statistical analysis

Analyses were conducted using Stata release 13.0 (StataCorp, College Station, TX, USA). First, socio-demographic characteristics were assessed by sex and EDS status (CES-D score ≥16 vs <16, based on mean score across visits). We tested mean differences between groups using t-tests and analysis of variance; relationships among categorical variables were evaluated with χ² tests. Second, mixed-effects regression on continuous CES-D total or on domain-specific score(s) was used to test the association between the three serum lipid exposure variables and depressive symptoms, controlling for potential confounders. Moderating effect of sex was tested by adding interaction terms to the multivariable mixed-effects regression models and stratifying by sex. The mixed-effects regression analyses are discussed in detail in Appendix I and in the following papers.77 A two-stage Heckman selection model was also used to test Hypothesis 2 whereby baseline CES-D total score was the predictor for each of the three serum lipid variables (TC, TCHDL-C and LDL-CHDL-C) modeled over time in a linear mixed-effects regression model. A sensitivity analysis was conducted to examine if the key findings were robust to the exclusion of statin users at baseline.

To account for potential selection bias in mixed-effects regression models (due to the non-random selection of participants with complete data from the target study population), a two-stage Heckman selection model was constructed, using a probit model to obtain an inverse mills ratio at the first stage (derived from the predicted probability of being selected, conditional on the covariates in the probit model, mainly baseline age, sex, race, poverty status and education), as was done in an earlier study.81 A type I error of 0.05 was used for all analyses, with P-values between 0.05 and 0.10 considered as borderline significant for main effects, and P-value < 0.10 considered significant for interaction terms, before multiple testing correction. The latter was done using a family-wise Bonferroni procedure, with family defined by CES-D total or subscale scores, assuming content-wise independence. As defined in a methodological report, a ‘family’ of inferences in the context of confirmatory analysis is ‘any collection of inferences for which it is meaningful to take into account some combined measure of error’.84 Thus, accounting for three main exposures assuming that a family is each of the subscales and the total score type I error was reduced to 0.05/3 = 0.017 for main effects and 0.10/3 = 0.033 for interaction terms (that is, two-way and three-way interactions). A similar approach was followed in a recent study.85

RESULTS

EDS across visits had an estimated unweighted prevalence of 29.2% in men and 37.9% in women (P < 0.001, χ² test; Table 1). Participants classified as EDS⁺ differed significantly from their EDS⁻ counterparts. Most notably, they had lower income based on PIR < 125%, they were more likely unemployed, and had lower educational attainment. Among women, EDS⁺ (vs EDS⁻) was associated with a lower likelihood of marriage (22.6 vs 32.1%, P = 0.002), and a higher proportion of current smokers (50.5 vs 34.7%, P < 0.001) or users of any type of illicit drugs (41.0 vs 30.4%, P = 0.001). Moreover, mean

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| Table 1. Characteristics of HANDLS study participants by sex and Center for Epidemiologic Studies Depression Scale (CES-D) score (mean across visits)^a |
|---|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Men vs women | Low vs high CES-D score among men | Low vs high CES-D score among women |
| % | < 16 (n = 587) | ≥ 16 (n = 240) | All men (n = 827) | < 16 (n = 675) | ≥ 16 (n = 424) | All women (n = 1099) | p^b | &<box>0.001</box> | &<box>0.001</box> | &<box>0.001</box> |
| Depressive symptoms | | | | | | | | | | |
| CES-D, mean ± s.e.m. | 8.3 ± 0.2 | 23.0 ± 0.4 | 12.5 ± 0.3 | 8.00 ± 0.17 | 24.1 ± 0.34 | 14.2 ± 0.3 | | | | |
| TC, mean ± s.e.m. | 182.9 ± 1.9 | 186.0 ± 3.0 | 183.8 ± 1.6 | 190.1 ± 1.5 | 189.6 ± 2.0 | 189.9 ± 1.2 | | | | |
| LDL-C, mean ± s.e.m. | 4.08 ± 0.06 | 4.17 ± 0.12 | 4.11 ± 0.06 | 3.60 ± 0.04 | 3.76 ± 0.06 | 3.66 ± 0.04 | | | | |
| Socio-demographic and lifestyle factors | | | | | | | | | |
| Age (years), mean ± s.e.m. | 48.6 ± 0.4 | 48.3 ± 0.6 | 48.5 ± 0.3 | 48.6 ± 0.4 | 48.0 ± 0.4 | 48.4 ± 0.3 | | | | |
| African-American, % | 58.4 | 60.8 | 59.1 | 57.3 | 55.0 | 56.4 | | | | |
| Marital status, % | | | | | | | | | |
| Currently married | 36.3 | 28.8 | 34.1 | 32.1 | 22.6 | 28.5 | | | | |
| Education, % | | | | | | | | | |
| < HS | 6.6 | 11.3 | 8.0 | 5.0 | 7.6 | 6.0 | | | | |
| > HS | 38.3 | 21.7 | 33.5 | 41.3 | 26.2 | 35.5 | | | | |
| Missing | 0.0 | 0.0 | 0.0 | 0.0 | 0.2 | 0.1 | | | | |
| Body mass index, kg/m^2; mean ± s.e.m. | 28.0 ± 0.2 | 27.9 ± 0.4 | 28.0 ± 0.2 | 31.4 ± 0.3 | 31.1 ± 0.4 | 31.3 ± 0.26 | | | | |
| Dietary factors, daily intakes | | | | | | | | | |
| Energy, kcal | 2290 ± 44 | 2302 ± 75 | 2364 ± 38 | 1740 ± 29 | 1734 ± 36 | 1738 ± 23 | | | | |
| Total carotenoids, mg/1000 kcal | 3847 ± 192 | 3164 ± 236 | 3649 ± 153 | 4371 ± 187 | 3817 ± 226 | 4158 ± 145 | | | | |
| n-3 PUFAs included DHA+EPA+n-3 DPA+ALA. n-6 PUFAs included AA+LA. | | | | | | | | | |

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; CES-D, Center for Epidemiologic Studies-Depression Scale; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; HANDLS, Healthy Aging in Neighborhoods of Diversity Across the Life Span; HDL-C, high-density lipoprotein-cholesterol; HS, high school; LA, linoleic acid; LDL-C, low-density lipoprotein-cholesterol; n-3, omega-3; n-6, omega-6; PIR, poverty income ratio; PUFAs, polyunsaturated fatty acids; TC, total cholesterol. ^Values are percent or mean ± s.e.m. P-value was based on independent samples t-test when row variable is continuous and x^2-test when row variable is categorical. ^n-3 PUFAs included DHA+EPA+n-3 DPA+ALA. n-6 PUFAs included AA+LA.
body mass index was higher among women vs men (31.3 vs 28.0), but was not associated with EDS status.

Sex differences were also detected for marital status (28.5% in women, 34.1% in men, \( P = 0.017 \)), PIIR \( \geq 125\% \) (60.3% in men, 54.1% in women, \( P < 0.001 \)), employed (52.8% in men, 44.2% in women, \( P < 0.001 \)), current smoking status (49.9% in men vs 40.8% in women) and current use of any illicit drug (57.3% in men vs 34.5% in women).

Of the three serum lipid exposures of interest, women had a higher mean TC (189.9 vs 183.8, \( P = 0.002 \)) and higher proportion \( > 200 \text{ mg dl}^{-1} \) (37.9 vs 31.9, \( P < 0.001 \)) compared with men. However, both atherogenic indices were significantly higher among men (TCHDL-C \( \rightarrow \) 4.11 vs 3.66, \( P < 0.001 \); LDL-CHDL-C \( \rightarrow \). 2.45 vs 2.17, \( P < 0.001 \); Table 1). Moreover, \( \sim 14.7\% \) of the selected sample were statin users. Statin use did not differ by sex or EDS status. Importantly, statin use was not associated with baseline CES-D score or its rate of change over time. This also pertained to the subscales of CES-D. Thus, statin use was not an important confounder in the relationship between serum lipids in longitudinal change in depressive symptoms. Its inclusion in the models did not alter the key findings. (data not shown)

Overall dietary quality measured by the HEI-2010 was significantly lower among men compared with women and significantly lower among both men and women with EDS + status compared with EDS - (Table 1). EDS + status was also associated with lower intakes of energy-adjusted total carotenoids (men), vitamin C (women), vitamin E (both), vitamin B-6 and folate (women). Women had higher energy-adjusted intakes of total carotenoids and vitamin E compared with men, though the reverse pattern was true for total energy intake.

Using a mixed-effects regression model without adjustment for covariates or inclusion of exposure variables, the annual rate of change in CES-D score (sex-stratified), mixed-effects linear regression analysis, HANDLS study, 2004–2013

### Table 2.

| Fixed effect | Men: Model 1* | Women: Model 2* |
|--------------|--------------|----------------|
| Intercept \((\gamma_0)\) for \( \text{TC}_{\text{low}} \) | +15.92 ± 1.78 | +15.85 ± 1.76 |
| Time \((\gamma_1)\) for \( \text{TC}_{\text{high}} \) | +1.18 ± 0.50 | +0.83 ± 0.49 |
| Age \((\gamma_2)\) | -0.07 ± 0.03 | -0.06 ± 0.03 |
| \( \text{TC}_{\text{low}} \times \text{time} \) for \( \gamma_{01} \) | +0.01 ± 0.009 | +0.056 ± 0.009 |
| \( \text{TC}_{\text{low}} \times \text{time} \) for \( \gamma_{11} \) | -0.00 ± 0.009 | +0.06 ± 0.009 |
| \( \text{TC}_{\text{high}} \times \text{time} \) for \( \gamma_{01} \) | -0.03 ± 0.19 | -0.25 ± 0.22 |
| \( \text{TC}_{\text{high}} \times \text{time} \) for \( \gamma_{11} \) | +0.14 ± 0.16 | +0.23 ± 0.17 |

| Random effects | Men: Model 1* | Women: Model 2* |
|----------------|--------------|----------------|
| Level 1 residuals \((R_0)\) | 2.52 ± 0.49 | 4.69 ± 0.32 |
| Level 2 residuals | = 0.004 | = 0.001 |
| Linear slope \((\delta_0)\) | 1.46 ± 0.09 | 1.50 ± 0.09 |

### Abbreviations:
- CES-D, Center for Epidemiologic Studies-Depression Scale; HANDLS, Healthy Aging in Neighborhoods of Diversity Across the Lifespan; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; n-3, omega-3; n-6, omega-6; PUFAs, polyunsaturated fatty acids; TC, total cholesterol. *Models were further adjusted for other covariates (main effects and interaction with time). See Materials and Methods section for more details on covariate coding and model specifications. Time at baseline visit was set to zero. Baseline age was centered at 50 years, total energy intake at 2000 kcal per day, total carotenoid intake at 3 mg per 1000 kcal per d, vitamin C intake at 30 mg per 1000 kcal per day, vitamin A intake at 300 \( \mu \)g per 1000 kcal per day, vitamin E at 3 mg per 1000 kcal per day, vitamin B-6 at 0.8 mg per 1000 kcal per day, vitamin B-12 at 3 \( \mu \)g per 1000 kcal per day, folate at 170 \( \mu \)g per 1000 kcal per day, n-3 PUFAs = n-3 PUFAs at 0.11; Healthy Eating Index-2010 was centered at 42. \( N \) = number of participants in the analysis; \( \gamma \pm \) s.e. refer to the estimated regression coefficients from the mixed-effects regression models with their associated standard error. Random effects are presented only for TC models, but were comparable in the remaining models.

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change over time in the CES-D score was estimated at 0.88 with 95% CI (0.78; 0.99), \( P < 0.001 \). Table 2 displays key findings from mixed-effects regression models with CES-D score as the main outcome and the three lipid exposures, stratified by sex and adjusting for multiple covariates. The fixed effects of baseline age indicate that younger participants at baseline had a higher CES-D score than older participants (\( \gamma_{\text{age}} > 0, P < 0.05 \)). Among men, the CES-D score increased over time (\( \gamma_{10} > 0, P < 0.050 \)). Importantly, among women, higher baseline atherogenic indices (both TC:HDL-C and LDL-C:HDL-C) were associated with a faster rate of increase in CES-D scores over time, after correction for multiple testing (\( \gamma_{11} > 0, P < 0.030 \)). The total CES-D scores’ trajectories over time by level of atherogenic indices among women are illustrated in Figures 1a and 1b. In contrast, the total CES-D score’s trajectory over time was not significantly altered by baseline TC level. These findings remained unaltered when excluding statin users, though slightly attenuated in the case of LDL-CHDL-C (\( P < 0.05 \), data not shown).

Findings from domain-specific analyses among women (Table 3) indicated that atherogenic indices were associated with a faster rate of increase in depressed affect (component 2: both indices) and interpersonal problems (component 4: TC:HDL-C; \( P < 0.033 \)), findings illustrated in Figures 2a–c. No significant associations between baseline atherogenic indices and CES-D components were found among men (Table 4). Sex differences were significant for both atherogenic indices for depressed affect using a three-way interaction to test sex differences in the trajectories of this domain over time by levels of exposure (\( P = 0.023 \) for TC:HDL-C exposure and \( P = 0.028 \) for LDL-CHDL-C exposure). Moreover, after excluding statin users among women, TC\(_{\text{low}}\) was linked to slower increase in depressed affect over time (\( \gamma_{11} < 0; P < 0.033 \)), whereas TC\(_{\text{high}}\) was asso-

![Graph](image1.png)

**Figure 1.** (a) Predictive margins of CES-D total score, mixed-effects regression model with TC:HDL-C atherogenic index, controlling for selected covariates, among women. (b) Predictive margins of CES-D total score, mixed-effects regression model with LDL-CHDL-C atherogenic index, controlling for selected covariates, among women. CES-D, Center for Epidemiologic Studies-Depression; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.
Table 3. Analysis of baseline atherogenic indices and longitudinal change in CES-D component scores among women, mixed-effects linear regression analysis, HANDLS study, 2004–2013

| Atherogenic index | X = LDL-C/HDL-C | X = TC/HDL-C |
|-------------------|-----------------|--------------|
|                   | Fixed effect    | Fixed effect |
|                   | γ ± s.e.e.       | P-value      | γ ± s.e.e.       | P-value      |
| Intercept (γ₀)    | 3.25 ± 0.09     | < 0.001      | 3.25 ± 0.09     | < 0.001      |
| Time (γ₁) for n₀ | 2.88 ± 0.13     | < 0.001      | 2.88 ± 0.13     | < 0.001      |
| Linear slope (γ₂) | 0.00 ± 0.00     | < 0.05       | 0.00 ± 0.00     | < 0.001      |
|                   |                 |              |                 |              |
| Intercept (γ₀)    | 2.97 ± 0.12     | < 0.001      | 2.95 ± 0.12     | < 0.001      |
| Time (γ₁) for n₁ | 3.11 ± 0.12     | < 0.001      | 3.11 ± 0.12     | < 0.001      |
| Linear slope (γ₂) | 0.25 ± 0.09     | < 0.001      | 0.25 ± 0.09     | < 0.001      |
|                   |                 |              |                 |              |
| Intercept (γ₀)    | 1.94 ± 0.05     | < 0.001      | 1.94 ± 0.05     | < 0.001      |
| Time (γ₁) for n₁ | 1.76 ± 0.08     | < 0.001      | 1.76 ± 0.08     | < 0.001      |
| Linear slope (γ₂) | 0.00 ± 0.00     | < 0.05       | 0.00 ± 0.00     | < 0.05       |
|                   |                 |              |                 |              |

Abbreviations: CES-D, Center for Epidemiologic Studies-Depression Scale; HANDLS, Healthy Aging in Neighborhoods of Diversity Across the Lifespan; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; n₃, omega-3; n₆, omega-6; PUFAs, polyunsaturated fatty acids; TC, total cholesterol. Models were further adjusted for other covariates (main effects and interaction with time). *See Materials and Methods section for more details on covariate coding and model specifications. Time at baseline visit was set to zero. Baseline age was centered at 50 years, total energy intake at 2000 kcal per day, total saturated fat intake at 3 mg per 1000 kcal per day, vitamin C intake at 100 mg per 1000 kcal per day, vitamin A intake at 3500 RE per 1000 kcal per day, vitamin E at 15 mg per 1000 kcal per day, vitamin B₆ at 0.8 mg per 1000 kcal per day, vitamin B₁₂ at 1.5 mcg per 1000 kcal per day, folate at 200 mcg per 1000 kcal per day, and various inflammatory markers. The interaction between age and time was included in the model. P-values were adjusted for multiple comparisons using the Bonferroni correction.
citated with faster increase in interpersonal problems (γ₁₁ > 0; P < 0.033).

Among men, a U-shaped pattern was found between TC and somatic complaints whereby TC_{low} and TC_{high} (vs TC_{medium}) were both associated with a faster rate of increase over time even though TC_{low} was linked to significantly lower score compared with TC_{medium} (Figure 3a; γ₁₀₁ > 0 (P < 0.033), γ₁₁₁ > 0 (P < 0.05) and γ₁₁₂ > 0, P < 0.033). After excluding statin users, the results remained similar. In contrast, and unlike its potential adverse effect on somatic complaints, TC_{low} at baseline was associated with a higher rate of increase over time on positive affect (component 3), indicating a better outcome when TC level is <160 mg dl⁻¹ when compared with TC_{medium} (160–200 mg dl⁻¹; Figure 3b).

None of the longitudinal associations were statistically significant when baseline CES-D total score was modeled as a predictor of change in lipid profile over time (Table 5). This finding indicates that the direction of the relationship in this sample is serum lipids → depressive symptoms rather than depressive symptoms → serum lipids.

DISCUSSION

The present study found that among adult women residing in Baltimore, MD, USA, higher levels of atherogenic indices were linked to faster increases in depressive symptom scores, particularly depressed affect and interpersonal problems. Three of 11 case–control studies1–15 corroborated our findings of a positive relationship between atherogenic indices and depression.9,11,12 Unlike the current study, many case–control studies tested only TC as the exposure7,17 and commonly found an inverse relationship between TC and mood disorders, particularly major depressive disorder.4,16 Furthermore, most did not utilize atherogenic indices but examined the metabolic syndrome and components14 or lipoprotein fractions as they relate to mood symptoms,12–14 with some showing an effect on somatic complaints, TClow at baseline was associated with low mood and increased risk of depression was related to both low LDL-C and/or HDL-C,18,19,32 whereas others yielded null or mixed findings.7,14,35 At least two studies examined the relationship between lipid profiles and depression in the opposite temporal direction. The first study conducted among 1186 male workers (19–68 years) who were followed for 5 years showed that higher baseline depressive symptoms, particularly psychomotor agitation, were associated with increased risk of incident metabolic syndrome and hypertriglyceridemia.4,18 The second study conducted in the Netherlands among 2126 adults followed for 2 years found that baseline depressive and anxiety symptoms predicted a decrease in HDL-C and a concomitant increase in waist circumference, thus predisposing to cardiovascular disease. In contrast, reduction in depressive symptoms did not correlate with a lipid profile improvement.112 A number of intervention studies examined the effects of cholesterol-lowering diets and medications, mainly statins, on affective disorders. In an earlier population-based intervention on ~300 middle-aged adults, depression and aggressive hostility were reduced significantly by consuming cholesterol-lowering diets, compared with controls.17 A meta-analysis of seven randomized controlled trials of statin use that included 2105 adults showed that statin use was linked to improvement in mood scores, thus refuting the evidence of negative effects of statins on psychological well-being.51 When examining the association in the reverse direction, an open-label prospective trial of 65 depressed in-patients was conducted whereby remission vs non-remission over 4–5 years was the primary exposure and lipid profile was the outcome. One key finding was that remission from depression was associated with a reduction in LDL-C/HDL-C ratio and thus a change in lipid profile towards a lesser atherogenic composition.48 Moreover, in our study, some findings emerged after exclusion of statin users among women, while others were attenuated (for example, LDL-C: HDL-C vs CES-D total score trajectory among women).

Despite the inclusion of both men and women in most reviewed studies, only some conducted sex-stratified analyses.4,9,22,24,33,34,39,46 Notably, in one large cross-sectional study, a higher depression prevalence was observed among women with HDL-C <35 mg dl⁻¹.22 In contrast, another study found that LDL-C was inversely related to depressive symptoms among women but not men, after controlling for adiposity and other cardiovascular and socio-demographic factors.33 A recent study also found that a higher TC (but not HDL-C) was associated with slower increase in depressive symptoms among Japanese older adults.35 In another large cohort study that stratified analyses by sex, and similar to our key finding, low HDL-C was associated to higher EDS prevalence (based on CES-D score ≥ 16) among women only. Both incident and prevalent EDS were linked to lower baseline LDL-C among men, particularly those who were at increased risk of depression by carrying the s/l or s/s genotype of the 5-serotonin transporter gene.49,50 The CNS, accounting only for 2% of body mass, contains 25% of body cholesterol. Cholesterol, being an integral part of cell membranes and a major myelin component, has a vital role in the development, function and stability of synapses. Low serum cholesterol may directly influence brain lipids and cell membrane

(70–89 years), TC was inversely related to risk of depression measured by the Zung Self-Rating Depression scale (score >48).40 A TC decline over 5 years was linked to incident depression on the basis of the third study also conducted among Finnish men (70–89 years).44 No other cohort studies examined atherogenic indices in relation to mood changes or incident depression. Some studies with TC as an exposure did not find associations with depression,37,41 whereas one found that higher TC was linked to greater risk of suicide attempts among depressed in-patients.43 However, several population-based cohort studies examined lipoprotein fractions in relation to well-being and psychosocial outcomes. Some confirmed the vascular depression hypothesis whereby lower HDL-C was associated with worse outcomes,42,45,46 whereas others yielded null or mixed findings.37,39,53 Among men, there was a U-shaped relationship between baseline TC and longitudinal increase in somatic complaints and a direct link between low TC and longitudinal putative improvement in positive affect compared with medium TC. A recent study using national data compared lipid profiles of severely depressed with mild or moderately depressed participants. Among men, there was also a U-shaped relationship between LDL-C and the odds of severe depression remained significant after adjustment for potential confounders.34 Baseline depressive symptoms were not longitudinally related to changes in TC or atherogenic indices in our study. These associations were independent of basic socio-demographic variables, as well as selected lifestyle and behavioral factors.

Among 12 prospective cohort studies37–48 that examined similar research questions, findings were mixed. In fact, in one of the largest cohort studies to date (N = 29 133),18 lower baseline TC was associated with low mood and increased risk of hospitalization for depression and death from suicide after 5–8 years of follow-up. This finding was corroborated by at least three other studies. In the first study conducted among 504 Japanese older adults, higher baseline TC was linked to slower increase in the Geriatric Depression Scale score over 4 years, among men only.39 In a study conducted among 421 older Finnish adult men...
Figure 2. (a) Predictive margins of CES-D component 2 score (depressed affect), mixed-effects regression model with TC:HDL-C atherogenic index, controlling for selected covariates, among women. (b) Predictive margins of CES-D component 4 (interpersonal problems), mixed-effects regression model with TC:HDL-C atherogenic index, controlling for selected covariates, among women. (c) Predictive margins of CES-D component 2 score (depressed affect), mixed-effects regression model with LDL-C:HDL-C atherogenic index, controlling for selected covariates, among women. CES-D, Center for Epidemiologic Studies-Depression; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.
### Table 4. Analysis of baseline atherogenic indices and longitudinal change in CES-D component scores among men, mixed-effects linear regression analysis, HANDBL study, 2004–2013

|                      | X = LDL-CHDL-C |                      | X = TCHDL-C |
|----------------------|---------------|----------------------|------------|
|                      | γ ± s.e.      | P-value              | γ ± s.e.   | P-value              |
| Y = CES-D component 1: somatic complaints | N = 826       | N' = 1319            | N = 826    | N' = 1319            |
| Fixed effect         |               |                      |            |                      |
| Intercept (γ₀₀ for n₀) | +8.20 ± 1.00  | < 0.001              | +8.20 ± 1.00 | < 0.001              |
| Time (γ₁₀ for n₁)    | +1.40 ± 0.23  | < 0.001              | +1.41 ± 0.24 | < 0.001              |
| Age (γ₂₀)            | −0.03 ± 0.02  | 0.037                | −0.03 ± 0.02 | 0.040                |
| Age × time (γ₃₀)     | +0.04 ± 0.004 | 0.34                 | +0.00 ± 0.004 | 0.34                 |
| Atherogenic index (γ₄₀ for n₀) | −0.19 ± 0.12  | 0.11                 | −0.07 ± 0.10  | 0.47                 |
| Atherogenic index (γ₄₁ for n₁) | −0.03 ± 0.03  | 0.36                 | −0.01 ± 0.02  | 0.71                 |
| Random effects       |               |                      |            |                      |
| Level 1 residuals (R₁₀) | 2.57 ± 0.14  | < 0.001              | 2.57 ± 0.14 | < 0.001              |
| Level 2 residuals    | 2.84 ± 0.13   | < 0.001              | 2.85 ± 0.13 | < 0.001              |
| Linear slope (c₀)   | 0.22 ± 0.10   | < 0.05               | 0.23 ± 0.10 | < 0.001              |
| Y = CES-D component 2: depressed affect | N = 824       | N' = 1317            | N = 824    | N' = 1317            |
| Fixed effect         |               |                      |            |                      |
| Intercept (γ₀₀ for n₀) | 6.98 ± 0.99   | < 0.001              | +7.00 ± 0.99 | < 0.001              |
| Time (γ₁₀ for n₁)    | 0.93 ± 0.23   | < 0.001              | +0.92 ± 0.24 | < 0.001              |
| Age (γ₂₀)            | −0.02 ± 0.02  | 0.35                 | −0.02 ± 0.02 | 0.37                 |
| Age × time (γ₃₀)     | +0.03 ± 0.004 | 0.48                 | +0.00 ± 0.004 | 0.48                 |
| Atherogenic index (γ₄₀ for n₀) | −0.21 ± 0.12  | 0.09                 | −0.07 ± 0.10  | 0.44                 |
| Atherogenic index (γ₄₁ for n₁) | −0.01 ± 0.03  | 0.67                 | −0.01 ± 0.02  | 0.63                 |
| Random effects       |               |                      |            |                      |
| Level 1 residuals (R₁₀) | 2.56 ± 0.13  | < 0.001              | 2.56 ± 0.13 | < 0.001              |
| Level 2 residuals    | 2.83 ± 0.13   | < 0.001              | 2.84 ± 0.13 | < 0.001              |
| Linear slope (c₀)   | 0.23 ± 0.10   | < 0.001              | 0.23 ± 0.10 | < 0.001              |
| Y = CES-D component 3: positive affect | N = 825       | N' = 1317            | N = 825    | N' = 1317            |
| Fixed effect         |               |                      |            |                      |
| Intercept (γ₀₀ for n₀) | 9.24 ± 0.61   | < 0.001              | +8.26 ± 0.61 | < 0.001              |
| Time (γ₁₀ for n₁)    | +0.58 ± 0.16  | < 0.001              | +0.57 ± 0.16 | < 0.001              |
| Age (γ₂₀)            | +0.02 ± 0.01  | 0.07                 | +0.03 ± 0.01 | 0.07                 |
| Age × time (γ₃₀)     | −0.004 ± 0.003 | 0.09             | −0.005 ± 0.003 | 0.09             |
| Atherogenic index (γ₄₀ for n₀) | +0.05 ± 0.07  | 0.53                 | +0.03 ± 0.06  | 0.55                 |
| Atherogenic index × time (γ₄₁ for n₁) | −0.02 ± 0.02  | 0.26                 | −0.02 ± 0.02  | 0.17                 |
| Random effects       |               |                      |            |                      |
| Level 1 residuals (R₁₀) | 1.64 ± 0.08  | < 0.001              | 1.64 ± 0.09 | < 0.001              |
| Level 2 residuals    | 1.66 ± 0.08   | < 0.001              | 1.66 ± 0.08 | < 0.001              |
| Linear slope (c₀)   | 0.20 ± 0.05   | < 0.001              | 0.20 ± 0.05 | < 0.001              |
| Y = CES-D component 4: interpersonal problems | N = 825       | N' = 1319            | N = 825    | N' = 1319            |
| Fixed effect         |               |                      |            |                      |
| Intercept (γ₀₀ for n₀) | +1.89 ± 0.04  | < 0.001              | +1.87 ± 0.35 | < 0.001              |
| Time (γ₁₀ for n₁)    | +0.39 ± 0.09  | < 0.001              | +0.39 ± 0.09 | < 0.001              |
| Age (γ₂₀)            | −0.01 ± 0.01  | 0.037                | −0.01 ± 0.01 | 0.038                |
| Age × time (γ₃₀)     | +0.02 ± 0.002 | 0.17                 | +0.00 ± 0.002 | 0.17                 |
| Atherogenic index (γ₄₀ for n₀) | −0.06 ± 0.04  | 0.14                 | −0.04 ± 0.03  | 0.27                 |
| Atherogenic index × time (γ₄₁ for n₁) | +0.01 ± 0.01  | 0.58                 | +0.00 ± 0.01  | 0.70                 |
| Random effects       |               |                      |            |                      |
| Level 1 residuals (R₁₀) | 1.05 ± 0.05  | < 0.001              | 1.06 ± 0.05 | < 0.001              |
| Level 2 residuals    | 0.84 ± 0.05   | < 0.001              | 0.84 ± 0.05 | < 0.001              |
| Linear slope (c₀)   | 0.06 ± 0.05   | < 0.001              | 0.06 ± 0.05 | < 0.001              |

Abbreviations: CES-D, Center for Epidemiologic Studies-Depression Scale; HANDBL, Healthy Aging in Neighborhoods of Diversity Across the Lifespan; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; n-3, omega-3; n-6, omega-6; PUFAs, polyunsaturated fatty acids; TC, total cholesterol. Models were further adjusted for other covariates (main effects and interaction with time). See Materials and Methods section for more details on covariate coding and model specifications. Time at baseline visit was set to zero. Baseline age was centered at 50 years, total energy intake at 2000 kcal per day, total caroteneoid intake at 3 mg per 1000 kcal per day, vitamin C intake at 30 mg per 1000 kcal per day, vitamin A intake at 300 RE per 1000 kcal per day, vitamin E at 3 mg per 1000 kcal per day, vitamin B-6 at 0.8 mg per 1000 kcal per day, vitamin B-12 at 3 µg per 1000 kcal per day, folate at 170 µg per 1000 kcal per day, n-3 PUFAs at 0.6 g per 1000 kcal per day. Healthy Eating Index-2010 was computed at 42. N = number of participants in the analysis; N' = total number of visits included in the analysis. Findings that were significant at a type I error of 0.05 are in bold. γ ± s.e.e. refer to the estimated regression coefficients from the mixed-effects regression models with their associated standard error.
fluidity, reducing serotonergic neurotransmission leading to mood and behavioral disorders. Cholesterol level may also be a ‘bystander’ for omega-3 fatty acid levels rather than underlying suicide or self-harm. Sudden fall in cholesterol after delivery currently serves as a ‘natural model’ for the cholesterol–postpartum mood relationship. Adverse psychological changes associated with cholesterol-lowering dietary and drug treatments might be due to effects on intakes and tissue concentrations of omega-3 fatty acids, and not due to a reduction of cholesterol levels. Docosahexaenoic acid, an omega-3 fatty acid obtained

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**Figure 3.** (a) Predictive margins of CES-D domain 1 score (somatic complaints), mixed-effects regression model with TC, categorical, controlling for selected covariates, among men. (b) Predictive margins of CES-D domain 3 score (positive affect), mixed-effects regression model with TC, categorical, controlling for selected covariates, among men. CES-D, Center for Epidemiologic Studies-Depression; TC, total cholesterol.
from fish consumption can affect synaptic function and cognitive abilities by providing plasma membrane fluidity at synaptic regions.84 Nevertheless, our study controlled for n-3 PUFA exposure, relative to n-6 PUFA without altering the key findings.

Our study has several notable strengths. First, the prospective cohort study design allows one to ascertain temporality of associations between serum lipids and depression. In fact, our analyses found significant associations in one temporal direction (that is, lipids → depression) but not the other (depression → lipids). Second, the sample size was large enough to allow for sex stratification without major loss in statistical power. Third, mixed-effects regression models were used adjusting for a large number of potentially confounding covariates. Despite these strengths, our study is also limited by potential selection bias due to non-

Table 5. Analysis of baseline CES-D score (X) and longitudinal change in total cholesterol (TC) and atherogenic indices (Y): sex-stratified mixed-effects linear regression analysis, HANDLS study, 2004–2013

|                           | Men: Model 1a | Women: Model 2a |
|---------------------------|---------------|-----------------|
|                           | γ ± s.e.       | P-value         | γ ± s.e.       | P-value         |
| Y = TC                    |                |                 |                |                 |
| Fixed effect              |                |                 |                |                 |
| Intercept (γ0, for n0)    | +177.5 ± 12.0  | < 0.001         | +209.1 ± 8.5   | < 0.001         |
| Time (γ10 for n1)         | +3.67 ± 2.73   | 0.18            | −1.53 ± 1.82   | 0.40            |
| Agebase (γ20)            | +0.11 ± 0.20   | 0.58            | +0.75 ± 0.14   | < 0.001         |
| Agebase × time (γ30)     | −0.01 ± 0.05   | 0.88            | −0.014 ± 0.031 | 0.65            |
| CES-D (γ40, for n0)      | −0.17 ± 0.24   | 0.47            | −0.04 ± 0.16   | 0.78            |
| CES-D × time (γ51, for n1) | +0.05 ± 0.06  | 0.35            | +0.02 ± 0.03   | 0.49            |
| Random effects            |                |                 |                |                 |
| Level 1 residuals (R0)   | 29.24 ± 1.55   | < 0.001         | 25.66 ± 0.68   | < 0.001         |
| Level 2 residuals        |                |                 |                |                 |
| Intercept (β0)           | 33.1 ± 1.5     | < 0.001         | 29.00 ± 1.04   | < 0.001         |
| Linear slope (β1)        | 1.61 ± 0.53    | < 0.001         | 0.00 ± 0.00    | < 0.001         |
| Y = LDL-C/HDL-C ratio    |                |                 |                |                 |
| Fixed effect              |                |                 |                |                 |
| Intercept (γ0, for n0)    | +1.49 ± 0.30   | < 0.001         | +2.01 ± 0.19   | < 0.001         |
| Time (γ10 for n1)         | +0.07 ± 0.06   | 0.22            | −0.08 ± 0.04   | 0.035           |
| Agebase (γ20)            | −0.01 ± 0.00   | 0.25            | +0.00 ± 0.00   | 0.29            |
| Agebase × time (γ30)     | −0.001 ± 0.001 | 0.49            | −0.000 ± 0.001 | 0.88            |
| CES-D (γ40, for n0)      | −0.01 ± 0.01   | 0.17            | +0.00 ± 0.00   | 0.31            |
| CES-D × time (γ51, for n1) | +0.01 ± 0.00  | 0.48            | +0.00 ± 0.00   | 0.48            |
| Random effects            |                |                 |                |                 |
| Level 1 residuals (R0)   | 0.59 ± 0.02    | < 0.001         | 0.52 ± 0.01    | < 0.001         |
| Level 2 residuals        |                |                 |                |                 |
| Intercept (β0)           | 0.93 ± 0.03    | < 0.001         | 0.71 ± 0.02    | < 0.001         |
| Linear slope (β1)        | 0.00 ± 0.00    | < 0.001         | 0.00 ± 0.00    | < 0.001         |
| Y = TC/HDL-C ratio       |                |                 |                |                 |
| Fixed effect              |                |                 |                |                 |
| Intercept (γ0, for n0)    | +2.48 ± 0.38   | < 0.001         | +3.36 ± 0.25   | < 0.001         |
| Time (γ10 for n1)         | +0.13 ± 0.08   | 0.09            | −0.13 ± 0.05   | 0.007           |
| Agebase (γ20)            | −0.01 ± 0.01   | 0.26            | +0.01 ± 0.00   | 0.23            |
| Agebase × time (γ30)     | −0.000 ± 0.001 | 0.84            | −0.001 ± 0.001 | 0.55            |
| CES-D (γ40, for n0)      | −0.00 ± 0.01   | 0.58            | +0.01 ± 0.00   | 0.25            |
| CES-D × time (γ51, for n1) | +0.00 ± 0.00  | 0.41            | +0.00 ± 0.00   | 0.38            |
| Random effects            |                |                 |                |                 |
| Level 1 residuals (R0)   | 0.82 ± 0.03    | < 0.001         | 0.69 ± 0.02    | < 0.001         |
| Level 2 residuals        |                |                 |                |                 |
| Intercept (β0)           | 1.14 ± 0.04    | < 0.001         | 0.90 ± 0.03    | < 0.001         |
| Linear slope (β1)        | 0.00 ± 0.00    | < 0.001         | 0.00 ± 0.02    | < 0.001         |

Abbreviations: CES-D, Center for Epidemiologic Studies-Depression Scale; HANDLS, Healthy Aging in Neighborhoods of Diversity Across the Lifespan; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; n-3, omega-3; n-6, omega-6; PUFA, polyunsaturated fatty acids; TC, total cholesterol. "Models were further adjusted for other covariates (main effects and interaction with time). See Materials and Methods section for more details on covariate coding and model specifications. Time at baseline visit was set to zero. Baseline age was centered at 50 years, total energy intake at 2000 kcal per day, total carotenoid intake at 3 mg per 1000 kcal per day, vitamin C intake at 30 mg per 1000 kcal per day, vitamin A intake at 300 RE per 1000 kcal per day, vitamin E at 3 mg per 1000 kcal per day, vitamin B-6 at 0.8 mg per 1000 kcal per day, vitamin B-12 at 3 μg per 1000 kcal per day, folate at 170 μg per 1000 kcal per day, n-3 PUFA n-6 PUFA at 0.11. Healthy Eating Index-2010 was centered at 42. N = number of participants in the analysis; N = total number of visits included in the analysis. Findings that were significant at a type I error of 0.05 are in bold. γ ± s.e.e. refer to the estimated regression coefficients from the mixed-effects regression models with their associated standard error."
participation or missing data on key covariates compared with the initially sampled group of individuals. However, the use of two-stage Heckman selection models minimized this bias. Furthermore, even though the key exposures were directly measured, the outcome and many of the covariates were self-reported, with potential for measurement error leading to residual confounding.

In summary, atherogenic indices were linked to a faster rate of increase in depressive symptoms among women only. Future intervention studies should examine changes in atherogenic indices with lipid-lowering treatment and how such changes may affect mood, particularly among women. Future longitudinal studies with at least three waves of data should also address the potential mediating effects of cardiovascular disease and type 2 diabetes in the associations between serum lipids and depressive symptoms. Finally, more studies are needed to uncover gene–atherogenic index interactions and their effect on depressive symptoms and mood disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX I

The mixed-effects regression models can be summarized as follows:

Multi-level models vs composite models

\[ Y_{ij} = \pi_{0i} + \pi_{1i} \text{Time}_{ij} + \sum_{a=1}^{2} \gamma_{0a} X_{a|ij} + \xi_{ij} \]
\[ \pi_{0i} = \gamma_{00} + \gamma_{0a} X_{a|ij} + \sum_{a=1}^{2} \gamma_{1a} X_{a|ij} \text{Time}_{ij} \]
\[ \pi_{1i} = \gamma_{10} + \gamma_{1a} X_{a|ij} + \sum_{a=1}^{2} \gamma_{2a} X_{a|ij} \text{Time}_{ij} + \zeta_{ij} \]

Where \( Y_{ij} \) is the outcome (CES-D total or domain-specific score) for each individual \( i' \) and visit \( j' \); \( \pi_{0i} \) is the level-1 intercept for individual \( i \); \( \pi_{1i} \) is the level-1 slope for individual \( i \); \( Y_{00} \) is the level-2 intercept of the random intercept \( \pi_{0i} \); \( \gamma_{10} \) is the level-2 intercept of the slope \( \pi_{1i} \); \( Z_{a|ij} \) is a vector of fixed covariates for each individual \( i \) that are used to predict level-1 intercepts and slopes and included baseline age (Age_base) among other covariates. \( X_{a|ij} \) represents the main predictor variables (1 absolute and 2 relative serum lipid exposures); \( \zeta_{0i} \) and \( \zeta_{1i} \) are level-2 disturbances; \( \epsilon_{ij} \) is the within-person level-1 disturbance. Of primary interest are the main effects of each exposure \( X_a \) (\( \gamma_{0a} \)) and their interaction with time (\( \gamma_{1a} \)), as described in a previous methodological paper.\(^7\)

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