Trends in TC/HDL and LDL/HDL Ratios across the Age Span: Data from the 2007-2018 National Health and Nutrition Examination Survey (NHANES)

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ABSTRACT

Background. Cholesterol levels in total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and triglyceride (TG) contribute to atherosclerosis and its clinical consequences.

Objectives. This study aimed to examine the trends in serum TC/HDL and LDL/HDL ratio across the age span.

Methods. This is an observational study. Blood lipid measurements, taken from 85,646 noninstitutionalized participants, aged 6 to 80, were obtained from the National Health and Nutrition Examination Survey (NHANES) study. We compared the TC/HDL and LDL/HDL ratio trends in three distinct cross-sectional surveys during 2007-2010, 2011-2014, and 2015- 2018.

Results. Cholesterol ratios changed by age and differed by sex. Mean TC/HDL ratios declined from 4.03 (95% CI, 4.01-4.05) in 2007-2010, to 3.84 (95% CI, 3.81-3.87) in 2015-2018 ($p<.05$ for linear trend) in male; mean TC/HDL ratios declined from 3.69 (95% CI, 3.67-3.70) in 2007- 2010, to 3.45 (95% CI, 3.42-3.47) in 2015-2018 ($p<.05$ for linear trend) in female. Mean LDL/HDL ratios declined from 2.30 (95% CI, 2.28-2.32) in 2007-2010, to 2.18 (95% CI, 2.15- 2.20) in 2015-2018 ($p<.05$ for linear trend) in male; mean LDL/HDL ratios declined from 2.04 (95% CI, 2.02-2.06) in 2007-2010, to 1.96 (95% CI, 1.94-1.98) in 2015-2018 ($p<.001$ for linear trend) in female.

Conclusions. Between 2007 and 2018, favorable trends in lipid ratio levels were observed among noninstitutionalized residents in the US.

Keywords. Serum lipids; aging; lipoprotein ratio; cholesterol; NHANES

ABBREVIATIONS

HDL-C = high-density lipoprotein LDL-C = low-density lipoprotein; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol; TG = triglyceride

INTRODUCTION

The benefits of managing blood cholesterol levels to patients with or at risk of developing cardiovascular disease are well documented [1]. Over the past decades, population-wide prevention of coronary heart disease has included guidelines intended to improve overall serum lipid concentrations in clinical practice [2-4]. For example, optimal lipid levels are among few risk factors that define a 10-year individual risk of fatal non-coronary atherosclerotic disease and fatal coronary heart disease, which in return helps clinicians make decisions about the type and dosage of the treatment (e.g., statin therapy, PCSK9).[1] Other risk models include the Systematic COronary Risk Evaluation (SCORE) [5], a European cardiovascular disease risk assessment model, and the recently published American College of Cardiology (ACC) and American Heart Association (AHA) Pooled Cohort Equations CV Risk Calculator calculates, a 10-year atherosclerotic cardiovascular disease (ASCVD) risk assessment model [6-10].

Studies [11-19] have been conducted to examine trends in serum lipid levels among the United States (US) population to inform physicians, the public health community, health care policy-makers, regulators, and standards-setting bodies. In both the youth [14,16,17] and adult [11,12,18,19] samples, results supported favorable trends in lipid levels such as a decrease in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG), and an increase in high-density lipoprotein cholesterol (HDL-C). In return, these results supported the therapeutic efforts in raising plasma HDL-C levels [20], reducing LDL-C levels [21,22], thereby reducing the risk of developing coronary heart disease in past decades.

Nonetheless, previous studies[11-19] examine trends in individual serum lipids but did not explore the trends of cholesterol ratios even though the concentration of plasma cholesterol is regulated by endogenous and exogenous pathways of cholesterol metabolism. While LDL-C cholesterol concentration has been the prime index of cardiovascular disease risk and the main target for therapy, data now suggest that TC/HDL cholesterol and LDL/HDL cholesterol ratios are risk indicators with greater predictive value than isolated parameters used independently [23].

The ratio of total cholesterol to high-density lipoprotein cholesterol (i.e., TC/HDL), known as the atherogenic or Castelli index, and the ratio of low-density lipoprotein to high- density lipoprotein cholesterol (i.e., LDL/HDL) are two important derived indicators from the lipid profile. Higher ratios mean a higher risk of heart disease. These lipoprotein ratios have been reported to have greater predictive power for cardiovascular risk than the isolated parameters and as a better mirror of the metabolic and clinical interactions between lipid fractions [7,23-25].The predictive capacity of these ratios is supported by data suggesting that an increase in HDL cholesterol is more prevalently associated with plaque regression, while a decrease in LDL cholesterol would slow down progression.[23] In clinical application, it is believed that mitigation of the level of lipoprotein ratio to a lower risk category will attenuate the risk of cardiovascular adverse events such as myocardial infarction [26,27]. There is, however, no consensus on which of these 2 indices is superior.

The purpose of this study was to examine the trends in serum lipoprotein ratio (TC/HDL and LDL/HDL) in noninstitutionalized US residents between 2007 and 2018 and to present the trends in levels of lipids across the age span (6 to 80 years old). Data on lipoprotein ratios can provide insight into current and future cardiovascular health.

METHOD STUDY DESIGN

This was an observational cross-sectional study. We used data from the National Health and Nutrition Examination Survey (NHANES) [28], which is a major program of the National Center for Health Statistics (NCHS), part of the Centers for Disease Control and Prevention (CDC). The NHANES has been collecting the health and nutritional status of adults and children in the US since 1960 using a mixed survey, physical examination, and laboratory (biological specimens) method. Briefly, the NHANES data were acquired from a stratified multistage probability sample of the US civilian noninstitutionalized resident population. The screener questionnaire and household interview questionnaires were administered in the home. Based on the survey participants' age at the time of screening, NHANES collected biological specimens (e.g., blood, urine) in the mobile examination center for laboratory analysis to provide detailed information about participants' health and nutritional status. Participants aged 12 years and older appointed to a morning session were asked to fast for 9 hours. A phlebotomist assessed the participant's fasting status before the blood draw.

Laboratory Measurements

Samples were received frozen and stored at -80ºC in the freezer until testing was performed. Upon completion of the analysis, specimens were stored at -70ºC and discarded after 1 year. All lipid analyses were analyzed according to a standardized protocol and can be found on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes).

Through the past decade, there were no major changes to the laboratory methods. The blood specimen were analyzed using the Roche/Hitachi Cobas 6000 chemistry analyzer in recent years. However, the TC, HDL-C, and TG were measured on the Roche modular P chemistry analyzer in the 2011-2012 cycle, and were measured on the Roche modular P and Roche Cobas 6000 chemistry analyzers in the 2013-2014 cycle.

The laboratory methods included quality control procedures. If control values are out of the acceptable range, the specimen was reanalyzed after recalibration. If the value exceeded the high limit of analytical measurement range (e.g., 0-120 mg/dL for HDL-C values), specimen was automatically diluted (e.g., net 1:2 for HDL-C) by the instrument, and reported accordingly. If a manual dilution was required, the specimen was diluted in normal saline, and the result was multiplied by the dilution factor. Serum LDL-C values were derived on study participants who aged 12 and above, were examined in the morning session only, and fasted at least 8.5 hours or more. LDL-C was calculated from measured values of TC, TG, and HDL-C according to the Friedewald calculation: LDL-C (in mg/dL) = [TC] – [HDL-C] – [TG/5].

NHANES 2007-2018 Data

NHANES data has since been released in two-year cycles. Data from six NHANES data cycles were included in the analysis, including 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016, 2017-2018. Of the initial 109,220 data records, 10,371 participants were removed because they were younger than 6 years old (no cholesterol data). Additional 11,404 participants were removed because they did not have blood tests. Because we observed some extreme lipoprotein values (e.g., triglyceride = 4,233 mg/dL), we flagged participants when their lipoprotein values were more than 1.5 interquartile ranges below the first quartile or above the third quartile of their corresponding sex and age group. As a result, additional 1,799 participants were classified as outliers and removed, resulting in a total sample of 85,646 for subsequent analysis. Figure 1 shows the flow diagram for the data cleaning procedure.

Approval for use of the NHANES data for this study was provided by the NCHS Research Ethics Review Board. Because this study involved secondary analysis of de-identified data, the Institutional Review Boards of the University of Wisconsin - Milwaukee determined that this study did not fall within the regulatory definition of research involving human subjects and did not require further IRB review.

Demographic Variables

Age in years was reported for survey participants at the time of the screening interview. Because the age of 80 and older was determined to be a disclosure risk, all participants aged 80 years and older were coded as '80' by the NHANES. In this study, age was categorized as 6-8, 9- 11 (children), 12-15, 16-19 (adolescent), 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-80 (adult) years.

We categorized survey years as 2007-2010, 2011-2014, and 2015-2018. Based on the analytical guidelines, each 2-year cycle, and any combination of 2-year cycles is a nationally representative sample [29].

Statistical Analyses

To compare lipoprotein ratio measures, a 2 (sex: male vs female) x 3 (survey periods: 2007-2010, 2011-2014, and 2015-2018) x 16 (age group) general linear model (GLM) analysis was used to test the hypothesis that these independent variables should be used to stratify lipoprotein ratio measurements. The significant level for the overall comparisons was set at alpha = 0.05. For independent variables found to have a significant main or interactive effect on lipid measurements, Scheffe pairwise post-hoc comparisons were conducted. Hypotheses of no survey trends in lipoprotein ratio values over the three survey periods were tested. Due to multiple comparisons, p-value less than 0.01 was considered significant for post-hoc comparisons. Descriptive statistics (including the mean and confidence

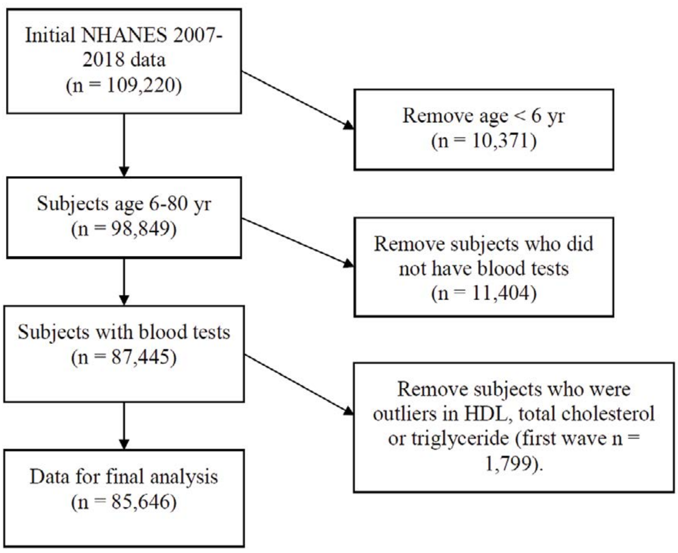

Figure 1: Data cleaning flow diagram

interval) of the TC/HDL, LDL/HDL lipoprotein ratios were tabulated for relevant strata. In general, the higher the ratio, the higher the risk of developing atherosclerotic cardiovascular disease. All analyses were performed using the SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM Corp).

RESULTS

Analytic Sample

The final data for analysis included 85,646 participants aged 6 to 80 years old. Among them, 52.6% of the sample were females. The majority of the sample was non-Hispanic white (44.6%), followed by non-Hispanic black (21.3%), Mexican American (14.3%), other Hispanic (10.0%), and others including multi-racial (9.8%). Data were balanced across each of the six, 2-year data collection cycles performed between 2007 and 2018 (2007-2010: 38.2%, 2011-2014: 36.0% and 2015-2018: 25.8%).

Overall GLM

Cholesterol ratios changed by age and differed by sex. The main effects (sex, age group, survey periods) and the interaction terms were all significant (p<0.001). Subsequently, to assist in clinical interpretation of lipoprotein ratios, we summarized lipoprotein ratio measures by sex and age group, and the linear trend of the survey years was tested for each age group.

TC/HDL Ratio

Table 1 summarizes means and 95% confidence intervals of the TC/HDL ratio by year (2007-2010, 2011-2014, and 2015-2018) and by sex (male and female). Overall, mean TC/HDL ratios

Table 1: Means and 95% confidence intervals of the TC/HDL ratio, aged 12 to 80 years, 2007-2018

TC/HDL Ratio		NHANES 2007-2010				NHANES 2011-2014				NHANES 2015-2018				p-value for linear trend		
				95% CI				95% CI				95% CI		2007-2010 to	2007-2010 to	2011-2014 to
Gender		N	Mean	L	U	N	Mean	L	U	N	Mean	L	U	2011-2014	2015- 2018	2015-2018
Male	6-8 yr	571	2.96	2.85	3.06	638	2.91	2.82	3.00	295	2.76	2.63	2.90	0.047	<0.001	0.007
	9-11 yr	588	3.13	3.03	3.24	631	3.03	2.93	3.12	288	2.98	2.84	3.11	0.078	0.033	0.712
	12-15 yr	688	3.15	3.05	3.24	708	3.04	2.96	3.13	594	3.03	2.93	3.12	0.065	0.042	0.959
	16-19 yr	659	3.45	3.36	3.55	600	3.30	3.20	3.39	528	3.31	3.20	3.41	0.019	0.032	0.995
	20-24 yr	451	3.83	3.71	3.94	519	3.67	3.57	3.77	360	3.64	3.52	3.76	0.104	0.067	0.923
	25-29 yr	449	4.33	4.21	4.45	459	3.94	3.84	4.05	411	3.86	3.74	3.97	<0.001	<0.001	0.616
	30-34 yr	508	4.61	4.50	4.72	594	4.50	4.40	4.59	416	4.45	4.33	4.56	0.444	0.233	0.855
	35-39 yr	615	4.88	4.78	4.98	573	4.54	4.44	4.63	409	4.69	4.58	4.81	0.001	0.175	0.331
	40-44 yr	670	4.88	4.78	4.97	652	4.62	4.53	4.71	444	4.48	4.37	4.60	0.011	<0.001	0.345
	45-49 yr	878	4.76	4.68	4.84	728	4.68	4.59	4.76	537	4.50	4.40	4.60	0.558	0.008	0.124
	50-54 yr	1056	4.88	4.81	4.96	966	4.47	4.40	4.55	647	4.38	4.29	4.47	<0.001	<0.001	0.607
	55-59 yr	1014	4.32	4.24	4.39	1012	4.13	4.06	4.20	781	4.06	3.97	4.14	0.013	0.001	0.527
	60-64 yr	1585	4.20	4.14	4.26	1615	4.18	4.12	4.23	1123	4.10	4.03	4.17	0.906	0.185	0.355
	65-69 yr	1478	3.92	3.85	3.98	1285	3.88	3.81	3.94	941	3.84	3.77	3.92	0.720	0.362	0.801
	70-74 yr	1447	3.97	3.90	4.03	1121	3.87	3.80	3.93	899	3.67	3.59	3.75	0.132	<0.001	0.003
	75-80 yr	2909	3.65	3.60	3.69	2379	3.53	3.48	3.58	1491	3.50	3.44	3.56	<0.001	<0.001	0.568
	Total	15566	4.03	4.01	4.05	14480	3.89	3.86	3.91	10164	3.84	3.81	3.87	<0.001	<0.001	0.032
Female	6-8 yr	528	3.22	3.11	3.33	511	3.08	2.97	3.18	255	2.99	2.85	3.14	0.012	0.001	0.368
	9-11 yr	545	3.29	3.18	3.40	568	3.17	3.08	3.27	279	2.92	2.78	3.06	0.070	<0.001	<0.001
	12-15 yr	580	3.09	2.99	3.19	663	3.11	3.02	3.20	496	2.93	2.82	3.03	0.854	0.003	<0.001
	16-19 yr	630	3.11	3.01	3.20	659	3.14	3.05	3.23	569	3.00	2.90	3.09	0.725	0.056	0.006
	20-24 yr	546	3.39	3.28	3.50	580	3.36	3.26	3.46	441	3.10	2.99	3.21	0.858	<0.001	<0.001
	25-29 yr	583	3.61	3.51	3.72	537	3.51	3.41	3.61	508	3.19	3.09	3.29	0.347	<0.001	<0.001
	30-34 yr	653	3.73	3.64	3.83	663	3.66	3.57	3.75	507	3.31	3.21	3.41	0.509	<0.001	<0.001
	35-39 yr	818	3.90	3.82	3.99	729	3.80	3.72	3.89	601	3.62	3.53	3.72	0.350	0.001	0.051
	40-44 yr	969	3.89	3.81	3.97	995	3.76	3.69	3.84	631	3.65	3.56	3.74	0.065	0.001	0.211
	45-49 yr	1288	3.98	3.91	4.05	1001	4.00	3.93	4.08	678	3.96	3.87	4.05	0.889	0.973	0.817
	50-54 yr	1174	4.05	3.98	4.12	1235	3.85	3.78	3.91	834	3.81	3.73	3.89	<0.001	<0.001	0.801
	55-59 yr	1129	3.94	3.87	4.02	1365	3.87	3.80	3.93	844	3.72	3.64	3.80	0.307	<0.001	0.024
	60-64 yr	1933	3.80	3.74	3.85	1742	3.69	3.63	3.74	1118	3.65	3.58	3.72	0.015	0.003	0.716
	65-69 yr	1380	3.81	3.74	3.88	1338	3.64	3.58	3.71	989	3.55	3.48	3.62	0.002	<0.001	0.198
	70-74 yr	1636	3.58	3.52	3.64	1402	3.52	3.46	3.59	792	3.44	3.35	3.52	0.400	0.013	0.212
	75-80 yr	2785	3.57	3.52	3.62	2353	3.47	3.42	3.52	1537	3.23	3.18	3.29	0.006	<0.001	<0.001
	Total	17177	3.69	3.67	3.70	16341	3.59	3.58	3.61	11079	3.45	3.42	3.47	<0.001	<0.001	<0.001

declined from 4.03 (95% CI, 4.01-4.05) in 2007-2010, to 3.89 (95% CI, 3.86-3.91) in 2011-2014, to 3.84 (95% CI, 3.81-3.87) in 2015-2018 (p<0.001 for linear trend) in male; mean TC/HDL ratios declined from 3.69 (95% CI, 3.67-3.70) in 2007-2010, to 3.59 (95% CI, 3.58-3.61) in 2011-2014, to 3.45 (95% CI, 3.42-3.47) in 2015-2018 (p<0.001 for linear trend) in female.

Figure 2 (A and B) shows the trend trajectories of the observed TC/HDL ratio across the age span. The means of TC/HDL

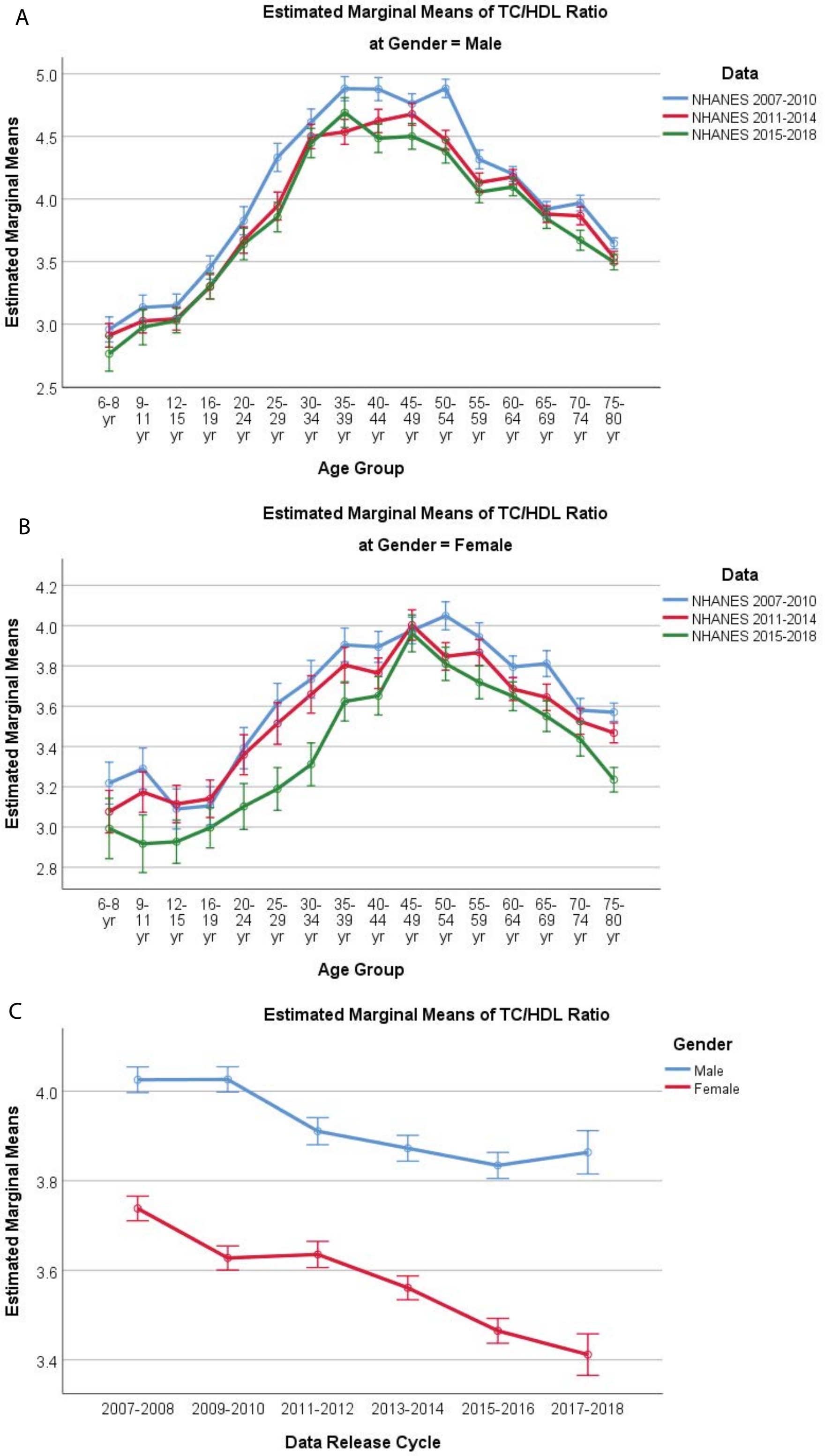

Figure 2: The trend trajectories of the observed TC/HDL ratio, aged 6 to 80 years, 2007-2018

ratios were lower for younger children, gradually increased to reach a plateau among adults that maintained through to mid-life, and then gradually declined from mid-life onwards. Figure 2-C shows the TC/HDL trends by data releasing year and by sex. Males had a higher TC/HDL ratio than females in most age groups (p<0.01), except in two age groups: (1) females had a higher TC/HDL ratio in age groups 6 to 9 years old (p<0.01) and (2) there were no differences between the sexes from age 10 to 15. Figure 2-C also shows the decreasing TC/HDL trends for both males and females across the years.

LDL/HDL Ratio

Table 2 summarizes means and 95% confidence intervals of the LDL/HDL ratio by year (2007-2010, 2011-2014, and 2015-2018) and by sex (male and female). Mean LDL/HDL ratios declined from 2.30 (95% CI, 2.28-2.32) in 2007-2010, to 2.23 (95% CI, 2.21-2.25) in 2011-2014, to 2.18 (95% CI, 2.15-2.20) in 2015-2018 (p<0.001 for linear trend) in male; mean LDL/HDL ratios declined from 2.04 (95% CI, 2.02-2.06) in 2007-2010, to 2.02 (95% CI, 2.00-2.04) in 2011-2014, to 1.96 (95% CI, 1.94-1.98) in 2015-2018 (p<0.001 for linear trend) in female.

Figure 3 (A and B) shows the trend trajectories of the observed LDL/HDL ratio across the age span. The means of LDL/HDL ratio were lower for younger children, gradually increased to reach a plateau in the adult life, and then gradually declined onwards. Figure 3-C shows the LDL/HDL trends by data releasing year and by sex. Males had a higher LDL/HDL ratio than females in most age groups (p<0.01), except that there

Table 2: Means and 95% confidence intervals of the LDL/HDL ratio, aged 12 to 80 years, 2007-2018

LDL/HDL Ratio		NHANES 2007-2010				NHANES 2011-2014				NHANES 2015-2018				p-value for linear trend			overall p-value
				95% CI				95% CI				95% CI		2007-2010 to	2007-2010 to	2011-2014 to	2007 to 2018
Gender		N	Mean	L	U	N	Mean	L	U	N	Mean	L	U	2011-2014	2015-2018	2015-2018	
Male	12-15 yr	336	1.70	1.61	1.79	339	1.70	1.61	1.79	367	1.62	1.53	1.71	-	-	-	p=0.163
	16-19 yr	326	1.87	1.78	1.97	286	1.86	1.76	1.96	369	1.88	1.80	1.97	-	-	-	p=0.909
	20-24 yr	215	2.28	2.17	2.40	238	2.12	2.01	2.22	244	2.12	2.02	2.23	-	-	-	p=0.068
	25-29 yr	225	2.63	2.52	2.74	216	2.33	2.22	2.44	244	2.26	2.15	2.36	0.007	<0.001	0.709	p<0.05
	30-34 yr	233	2.74	2.63	2.85	276	2.66	2.56	2.75	267	2.62	2.51	2.72	-	-	-	p=0.358
	35-39 yr	260	2.87	2.77	2.98	268	2.63	2.53	2.73	261	2.64	2.54	2.75	0.021	0.030	0.993	p<0.05
	40-44 yr	322	2.68	2.58	2.77	334	2.67	2.59	2.76	306	2.76	2.66	2.85	-	-	-	p=0.440
	45-49 yr	425	2.80	2.72	2.88	383	2.67	2.59	2.75	309	2.59	2.50	2.69	0.155	0.013	0.547	p<0.05
	50-54 yr	515	2.69	2.62	2.77	433	2.48	2.41	2.56	385	2.46	2.37	2.54	0.005	0.002	0.942	p<0.05
	55-59 yr	458	2.57	2.49	2.65	517	2.42	2.35	2.49	530	2.26	2.19	2.34	0.045	<0.001	0.032	p<0.05
	60-64 yr	757	2.28	2.22	2.35	763	2.31	2.25	2.37	682	2.26	2.19	2.32	-	-	-	p=0.650
	65-69 yr	699	2.07	2.00	2.13	589	2.17	2.10	2.23	546	1.97	1.90	2.04	0.097	0.148	<0.001	p<0.05
	70-74 yr	722	2.13	2.07	2.19	576	2.12	2.05	2.19	491	1.92	1.84	1.99	0.952	<0.001	<0.001	p<0.05
	75-80 yr	1357	2.05	2.00	2.09	1257	1.91	1.86	1.95	756	1.89	1.83	1.95	<0.001	<0.001	0.874	p<0.05
	Total	6850	2.30	2.28	2.32	6475	2.23	2.21	2.25	5757	2.18	2.15	2.20	<0.001	<0.001	0.004	p<0.05
Female	12-15 yr	256	1.68	1.58	1.79	317	1.67	1.58	1.76	338	1.59	1.50	1.68	-	-	-	p=0.071
	16-19 yr	289	1.70	1.60	1.80	317	1.76	1.67	1.86	380	1.67	1.59	1.76	-	-	-	p=0.150
	20-24 yr	249	1.84	1.74	1.95	270	1.93	1.83	2.03	274	1.76	1.66	1.86	0.392	0.463	0.029	p<0.05
	25-29 yr	255	2.01	1.90	2.11	255	1.92	1.82	2.03	308	1.78	1.69	1.88	0.453	0.002	0.092	p<0.05
	30-34 yr	326	2.15	2.05	2.24	317	1.98	1.88	2.07	324	1.88	1.78	1.97	0.028	<0.001	0.299	p<0.05
	35-39 yr	379	2.36	2.28	2.45	355	2.15	2.07	2.24	378	2.09	2.00	2.18	0.009	<0.001	0.645	p<0.05
	40-44 yr	412	2.10	2.02	2.18	482	2.10	2.02	2.17	350	2.15	2.06	2.24	-	-	-	p=0.621
	45-49 yr	575	2.21	2.14	2.28	444	2.32	2.24	2.40	434	2.34	2.26	2.42	0.152	0.072	0.943	p<0.05
	50-54 yr	606	2.34	2.27	2.41	572	2.25	2.18	2.32	474	2.21	2.13	2.28	0.249	0.057	0.726	p<0.05
	55-59 yr	570	2.26	2.19	2.33	631	2.16	2.10	2.23	552	2.19	2.12	2.26	-	-	-	p=0.166
	60-64 yr	950	2.06	2.01	2.12	857	2.13	2.07	2.18	609	2.11	2.04	2.17	-	-	-	p=0.197
	65-69 yr	621	1.99	1.93	2.06	685	2.04	1.98	2.11	563	1.89	1.82	1.96	0.535	0.090	0.004	p<0.05
	70-74 yr	882	1.90	1.85	1.96	696	1.86	1.80	1.92	414	2.03	1.95	2.11	0.606	0.042	0.005	p<0.05
	75-80 yr	1439	1.89	1.84	1.93	1181	1.87	1.82	1.92	887	1.71	1.66	1.77	0.809	<0.001	<0.001	p<0.05
	Total	7809	2.04	2.02	2.06	7379	2.02	2.00	2.04	6285	1.96	1.94	1.98	0.403	<0.001	<0.001	p<0.05

Abbreviations: LDL = low-density lipoprotein; HDL = high-density lipoprotein; CI = confidence interval; U = 95% CI upper limit; L = 95% CI lower limit

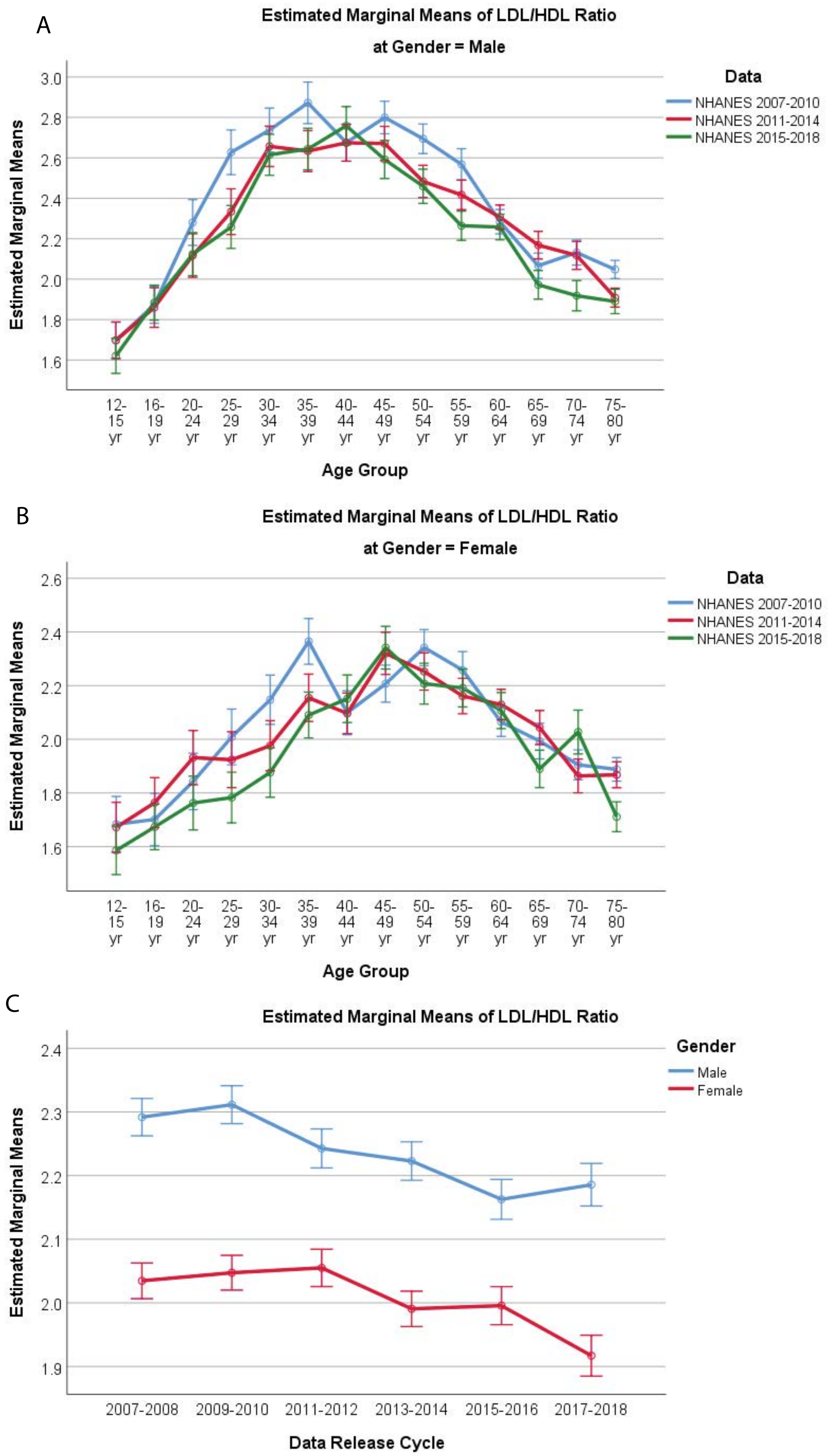

Figure 3: The trend trajectories of the observed LDL/HDL ratio, aged 12 to 80 years, 2007-2018

were no differences between the sexes from age 12 and 15 ($p>0.01$), and from age 75 to 79 ($p>0.01$). Figure 3-C also shows the decreasing LDL/HDL trends for both males and females across the years.

DISCUSSION

Cholesterol levels are important biomarkers associated with cardiovascular disease. In addition to predicting cardiovascular adverse events in patients with heart conditions,[6] these parameters are cost-effective markers to monitor abnormalities in lipoprotein metabolism and various disorders [27,30-36]. In this study, we examined the trends in serum lipoprotein ratio (TC/HDL and LDL/HDL) in more recent years between 2007 and 2018, and presented the trends in levels of lipids across the age span (6 to 80 years old).

Similar to previous studies [11-19], our results further supported the favorable decreasing trends in lipid ratios in the US population. As described by Perak et al., [17] it will be important to understand the reasons for the favorable lipid trends observed to acknowledge public health successes and plan for future efforts. Factors such as life habits, diet, obesity [37], cigarette smoking, alcohol use [38], exercise [39,40] and lipid-lowering medications are predictors of coronary disease and analyses the determinants of cholesterol and lipoprotein concentration. Carroll et al. [18] suggested that the favorable trend may be due in part to a decrease in consumption of trans-fatty acids or other healthy lifestyle changes, an increase in the percentage of adults taking lipid- lowering medications, changes in cigarette smoking and carbohydrate intake, and excluded that likelihood of due to the changes in physical activity, obesity, or intake of saturated fat. Nonetheless, data supported that the trends for lipids levels were generally directionally consistent across racial/ethnic groups and body mass index categories, [7] and also seen in adults in either taking or not receiving lipid-lowering medications [18].

Consistent with previous studies [41-43],we observed that younger people had lower TC/HDL and LDL/HDL values than mid-age adults did and that the values gradually declined at an older age. Consistent with Meysamie's study (2017) [41], females in adulthood tended to have lower TC/HDL and LDL/HDL ratios than males. Because Durgawale et al. [42] described ranges using 95% reference intervals instead of mean and percentile of the lipoprotein ratios, and Green et al. [43] reported inverted ratios (i.e., HDL/TC and HDL/LDL values), we had difficulties directly comparing results between studies. Nonetheless, LDL/HDL values reported by Durgawale et al.[42] seemed to be more stable/flat across the age span (e.g., range from 1.5 to 3.5) than within our study. Whereas the somewhat bell-shaped distribution curves we observed across the age span appear similar to results presented by Green et al. [43].

In investigating the physiological significance and clinical usefulness in cardiovascular prevention, Millan et al.[23] suggested that TC/HDL cholesterol and LDL/HDL cholesterol ratios are risk indicators with greater predictive value than isolated parameters used independently, particularly the former. In our study, the TC/HDL ratio correlated highly with LDL/HDL ratio (Pearson $r = 0.96$ in males and $r = 0.97$ in females). When comparing the TC/HDL ratio within each age group, all comparison p-values showed significant differences (in linear trends). In contrast, six out of 14 age groups in males and five out of 14 age groups in females did not show statistical significant differences when using the LDL/HDL ratio. Millan et al.[23] commented that the preference to use the TC/HDL cholesterol ratio is because there is no reliable calculation of LDL cholesterol when TG exceeds 300mg/dL. The calculation of LDL-C using the Friedewald equation is valid when TG is less than or equal to 400 mg/dL.

This study involves several limitations. First, this study included secondary data sources.The researchers were not in control of the data collection procedures. Missing values and data entry errors were not correctable. NHANES uses several quality assurance and quality control (QA/QC) protocols, which meet the 1988 Clinical Laboratory Improvement Act mandates, to monitor the quality of the analyses performed by the contract laboratories. For instance, contract laboratories randomly perform repeat testing on 2% of all specimens. Our analysis of trends was based on limited NHANES survey periods. Data from other future surveys are needed to confirm the favorable trends. We only examined the TC/HDL and LDL/HDL ratios, different cholesterol ratios such as the TC x TG/HDL ratio reported by Durgawale (2009)[42] could be explored. Several extraneous factors could influence cholesterol levels, such as lipid-lowering medications and race/ethnicity. We prioritized the maintenance of sample size within each stratum to achieve stable estimates of the lipoprotein ratio values. Future studies should endeavor to describe the ratio profile in US residents stratified by extraneous variables. Future studies are needed to fill the gaps in the fundamental knowledge of the factors that influence the changes in lipoprotein ratios across the age span.

CONCLUSION

Between 2007 and 2018, favorable trends in lipid ratio levels were observed among noninstitutionalized residents in the US.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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