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Relationship between heated tobacco product use and low-density lipoprotein cholesterol in Korean adults: a cross-sectional study using Korea National Health and Nutrition Examination Survey 2018-2021 (VII-1 and VIII)

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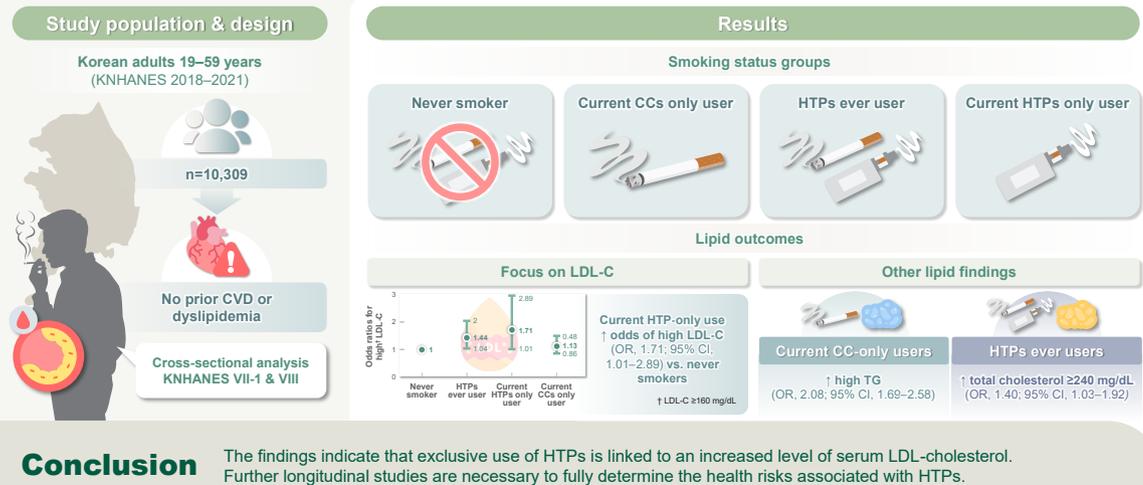
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Relationship between heated tobacco product use and low-density lipoprotein cholesterol in Korean adults: a cross-sectional study using Korea National Health and Nutrition Examination Survey 2018–2021 (VII-1 and VIII)

Study population & design

Korean adults 19–59 years (KNHANES 2018–2021)

n=10,309

No prior CVD or dyslipidemia

Cross-sectional analysis KNHANES VII-1 & VIII

Results

Smoking status groups

Never smoker | Current CCs only user | HTPs ever user | Current HTPs only user

Lipid outcomes

Focus on LDL-C

Current HTP-only use ↑ odds of high LDL-C (OR, 1.71; 95% CI, 1.01–2.89) vs. never smokers

† LDL-C ≥160 mg/dL

Other lipid findings

Current CC-only users ↑ high TG (OR, 2.08; 95% CI, 1.69–2.58)

HTPs ever users ↑ total cholesterol ≥240 mg/dL (OR, 1.40; 95% CI, 1.03–1.92)

Conclusion The findings indicate that exclusive use of HTPs is linked to an increased level of serum LDL-cholesterol. Further longitudinal studies are necessary to fully determine the health risks associated with HTPs.

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ABSTRACT

Background: The use of heated tobacco products (HTPs) among Korean adults has been steadily increasing since they were first introduced in 2017. It is known that smoking combustible cigarettes (CCs) adversely affects the serum lipid profile and increases the risk of cardiovascular disease. However, the health impacts of HTPs remain under-researched. This study, therefore, aims to explore the effects of HTP use on serum lipid levels.

Methods: This study involved 10,309 participants, selected from the Korea National Health and Nutrition Examination Survey VII-1 and VIII conducted between 2018 and 2021. Participants were categorized based on their smoking status: "HTPs ever user" included dual, triple, and past HTP users; "current HTPs only user" for those exclusively using HTPs; "current CCs only user" for those exclusively smoking CCs; and "never smoker." Logistic regression analysis was used to assess the impact of smoking type on serum lipid concentrations.

Results: The analysis revealed that the "HTPs ever user" group had a higher odds ratio (OR) for elevated total cholesterol compared to the "never smoker" group (OR, 1.40; 95% confidence interval [CI], 1.03–1.92). The likelihood of having high low-density lipoprotein (LDL)-cholesterol was greatest in the "current HTPs only user" group when compared to "never smokers" (OR, 1.71; 95% CI, 1.01–2.89).

Conclusion: The findings indicate that exclusive use of HTPs is linked to an increased level of serum LDL-cholesterol. Further longitudinal studies are necessary to fully determine the health risks associated with HTPs.

Keywords: Heat-Not-Burn Tobacco Product; E-Cigarette; Smoking; LDL Cholesterol; Dyslipidemias

Introduction

The smoking rate of combustible cigarettes (CCs) among adults in Korea has been continuously decreasing over the past 20 years. Specifically, the CCs smoking rate among men has decreased from 66.3% in 1998 to 30% in 2022. Among women, the rate initially was 6.5% in 1998, peaked at 7.5% in 2018, and subsequently declined to a record low of 5.0% in 2022 [1]. Additionally, the global prevalence of CC smoking has also declined over the past decades [2].

Conversely, the trend in the usage of heated tobacco products (HTPs) in Korea has diverged from the decreasing trend observed with CCs. Since the introduction of HTPs in 2017, the smoking rate for HTPs stagnated, moving from 6.2% in 2019 to 5.2% in 2020, and dropping further to 4.6% in 2021. However, it rose again to 5.9% in 2022. Specifically, the current usage rate of HTPs among men was 9.2% in 2022, and for women, it was 2.4%, marking increases of 1.9%p and 0.7%p, respectively, from 2021 [1]. Among adolescents, male smoking rates slightly decreased to 2.7% in 2023 from 3.2% the previous year, while female rates have seen a gradual increase from 0.8% in 2021 to 1.4% in 2023 [3]. Sales of HTP sticks in the country have also surged, rising from 78 million packs in 2017 to 444.1 million packs in 2021, and further to 538.6 million packs in 2022 [4]. Furthermore, a market report by Philip Morris International (PMI), a leading HTP producer, noted that Japan and South Korea held the largest HTP market shares in 2021 [5].

HTPs, also known as heat-not-burn tobacco products, involve heating specially treated tobacco leaves and additives to 350°C or less using electronic devices, without directly burning the tobacco. The resulting vapor is then inhaled by the user.

PMI claims that this method of "heating" rather than "burning" tobacco significantly reduces the emission of harmful substances by up to 95% compared to CCs [6]. In 2020, the US Food and Drug Adminis-

tration approved the IQOS 3 as a modified-risk tobacco product [7].

However, the World Health Organization maintains that there is insufficient research to confirm that HTPs are less harmful than CCs. It contends that smoking HTPs can expose users to a variety of harmful substances not present in CC smoke, and that the health effects of HTPs are not yet adequately studied [8]. HTPs are often recognized for their stylish design, reduced odor, and purported harm reduction features. They are predominantly used by young adults aged 19–39 [8,9]. In short, while HTPs are gaining popularity due to their perception of being less harmful, there is still limited evidence to support this.

Conversely, smoking CCs is well-known as a direct risk factor for cardiovascular diseases (CVD). This is partly due to the effects of nicotine, which alters serum lipid profiles by increasing triglycerides (TGs) and low-density lipoprotein-cholesterol (LDL-C), and decreasing high-density lipoprotein-cholesterol (HDL-C) among smokers [10]. Additionally, harmful and potentially harmful constituents (HPHCs) are produced when tobacco combusts, leading to an increase in free radicals and lipid peroxidation. These substances contribute to several mechanisms associated with CVD, including disturbances in lipid metabolism and endothelial dysfunction. This can result in the formation of atherosclerotic plaques and an increased risk of CVD [11].

It has been demonstrated that smoking HTPs increases both nicotine and biomarkers of carcinogens in the body [12]. The Korea Disease Control and Prevention Agency has conducted studies on behavioral changes among smokers following the introduction of electronic cigarettes (ECs) and HTPs, and investigated how different types of tobacco use affect the biomarkers of smokers [12]. The analysis revealed that concentrations of nicotine, cotinine, and OH-cotinine in HTPs single users were similar to those of CCs single users. Additionally, for dual (CCs+HTPs, CCs+ECs) and triple tobacco users (CCs+HTPs+ECs), levels of nicotine, cotinine, OH-cotinine, and NNAL—an indicator of ex-

posure to nicotine-derived nitrosamine ketone—were comparable to those found in CCs only users.

Harada et al. [13] analyzed the metabolomics of single users of CCs and HTPs. They found that metabolites in HTPs single users were more similar to those of CCs single smokers than to those of non-smokers. Notably, serum glutamate levels, which are associated with future CVD and arteriosclerotic plaques, were significantly higher among HTPs users.

Therefore, this study attempted to examine the basic characteristics of Korean HTPs users using data from the Korea National Health and Nutrition Examination Survey (KNHANES) and to determine whether there are differences in serum lipid levels compared to non-smokers and CCs smokers.

Methods

Study population and data collection

For this study, raw data from the KNHANES VII-1 and VIII (2018–2021) were used. Out of a total of 30,551 samples, 15,715 individuals aged 19–59 years were selected. Of these, 12,564 participants who had not been diagnosed with dyslipidemia, stroke, myocardial infarction, or angina were further filtered. Finally, 10,309 individuals without missing values for the main variables were chosen as the final subjects for this study.

Study variables

Smoking status was classified as follows: "HTPs ever user" for dual users (HTPs & CCs, HTPs & ECs), triple users (HTPs, CCs & ECs), and past HTPs users; "current HTPs only user" for those who currently smoke only HTPs, without using CCs or ECs; "current CCs only user" for those who currently smoke only CCs, without using HTPs or ECs; and "never smoker" for individuals who have never smoked at all.

Serum lipid concentrations, which are dependent variables, were categorized as follows: total cholesterol (TC) was classified as "normal" if below 200 mg/dL, "borderline" if between 200 mg/dL and 240 mg/dL, and "high" if above 240 mg/dL. HDL-C levels were classified as "low" if below 40 mg/dL for men and below 50 mg/dL for women, and "normal" if above 40 mg/dL for men and above 50 mg/dL for women. LDL-C levels were considered "normal" if below 130 mg/dL, "borderline" if between 130 mg/dL and 160 mg/dL, and "high" if above 160 mg/dL. Lastly, TGs were categorized as "normal" if below 150 mg/dL, "borderline" if between 150 mg/dL and 200 mg/dL, and "high" if above 200 mg/dL.

Covariates were defined as follows: Sex was classified as "men" and "women." Age groups included "19–29 years," "30–39 years," "40–49 years," and "50–59 years." Educational levels were categorized as "elementary school graduate or lower," "middle school graduate," "high school graduate," and "college graduate or more." Household income was classified into "low," "mid-low," "mid-high," and "high" based on income quartiles. The number of household members was divided into two groups: "living alone (yes)" or "living together (no)." Binge

drinking frequency was classified as "not at all," "monthly," "weekly," and "daily." Physical activity was classified as "yes" if moderate-intensity exercise was performed for more than 150 minutes per week, or if more than 75 minutes of high-intensity physical activity were performed. "No" was assigned if these thresholds were not met. Body mass index (BMI) was categorized as "underweight" for those with a BMI below 18.5 kg/m^2, "normal" for 18.5–22.9 kg/m^2, "overweight" for 23.0–24.9 kg/m^2, and "obese" for those with a BMI above 25.0 kg/m^2. High blood pressure and diabetes mellitus were classified as "yes" or "no" based on whether they had been diagnosed by a doctor.

Statistical analysis

A complex sample analysis was performed for this study, taking into account the complex sample design of the original KNHANES data. The steps of the analysis are as follows: First, a chi-square test (Rao-Scott χ^2 test) was conducted to examine the general characteristics and serum lipid concentrations of the study subjects and to assess differences in serum lipid levels according to smoking type. Second, a general linear model analysis was used to compare the average serum lipid concentrations by smoking type. Third, logistic regression analysis was conducted to evaluate the effect of smoking type on serum lipid concentration.

Statistical analysis was performed using IBM SPSS Statistics ver. 26.0 (IBM Corp.), with statistical significance set at a P-value of 0.05.

Results

General characteristics

The characteristics of the study subjects are summarized in Table 1. A chi-square test was conducted to examine the general characteristics and to assess whether there were significant differences according to smoking type. The results showed that all general characteristics differed significantly by smoking type (P<0.001).

The sex distribution by smoking type revealed a higher proportion of women among non-smokers, while there were more men among overall smokers. In terms of age, the group that smoked only CCs was the oldest, while the "HTPs ever user" group had a relatively higher proportion of individuals in their 20s and 30s. The "current HTPs only user" group had the highest proportion of individuals in their 40s, while the "current CCs only user" group and the never-smoker group had relatively more individuals in their 50s.

Regarding education level, the highest percentage of college graduates or higher was found in the "current HTPs only user" group, while the "current CCs only user" group had the lowest percentage of college graduates or higher.

In terms of household income, the "current HTPs only user" group had the highest proportion of high-income earners, whereas the "current CCs only user" group had the highest proportion of low-income earners.

The percentage of individuals living alone was highest in the "HTPs ever user" group and lowest among never-smokers. The frequency of

Table 1. General characteristics

Characteristic	Total	Smoking status				P-value
		HTPs ever user	Current HTPs only user	Current CCs only user	Never smoker	
No. of patients	10,309	671	179	1,853	7,606	
Sex						<0.001[a]
Male	3,945 (45.0)	541 (84.6)	137 (80.3)	1,520 (84.4)	1,747 (29.0)	
Female	6,364 (55.0)	130 (15.4)	42 (19.7)	333 (15.6)	5,859 (71.0)	
Age (y)	38.24±0.14	34.46±0.40[a]	39.18±0.68[bc]	39.69±0.32[c]	38.21±0.16[b]	<0.001[b]
19–29	2,517 (28.8)	222 (35.0)	25 (15.6)	399 (25.1)	1,871 (29.5)	<0.001[a]
30–39	2,478 (25.0)	245 (36.9)	60 (32.7)	395 (22.5)	1,778 (24.1)	
40–49	2,885 (25.7)	158 (21.4)	76 (43.4)	569 (28.8)	2,082 (24.8)	
50–59	2,429 (20.5)	46 (6.6)	18 (8.3)	490 (23.5)	1,875 (21.5)	
Education						<0.001[a]
≤Elementary	192 (1.7)	4 (0.6)	0	58 (3.0)	130 (1.5)	
Middle	414 (3.6)	23 (3.3)	3 (1.2)	124 (6.1)	264 (3.0)	
High	4,178 (41.4)	281 (42.4)	63 (34.0)	947 (51.3)	2,887 (38.7)	
≥College	5,525 (53.4)	363 (53.7)	113 (64.7)	724 (39.6)	4,325 (56.8)	
Household income						<0.001[a]
Low	796 (7.8)	57 (8.4)	7 (3.2)	196 (9.7)	536 (7.3)	
Mid-low	2,250 (21.8)	133 (18.6)	35 (20.8)	472 (25.2)	1,610 (21.2)	
Mid-high	3,246 (32.0)	220 (33.1)	53 (31.2)	609 (34.8)	2,364 (31.1)	
High	4,017 (38.5)	261 (39.8)	84 (44.8)	576 (30.3)	3,096 (40.4)	
Living alone						<0.001[a]
Yes	930 (9.1)	120 (18.3)	23 (12.0)	264 (13.2)	523 (6.9)	
No	9,379 (90.9)	551 (81.7)	156 (88.0)	1,589 (86.8)	7,083 (93.1)	
High-risk drinking						<0.001[a]
Never	4,561 (41.7)	122 (17.3)	41 (24.9)	340 (17.9)	4,058 (51.3)	
Monthly	3,667 (37.1)	274 (42.4)	64 (33.3)	632 (34.7)	2,697 (37.3)	
Weekly	1,615 (16.3)	204 (28.7)	58 (31.5)	611 (32.9)	742 (10.0)	
Daily	466 (4.9)	71 (11.5)	16 (10.3)	270 (14.6)	109 (1.4)	
Physical activity						<0.001[a]
Yes	4,926 (49.4)	364 (56.8)	80 (44.3)	810 (45.4)	3,672 (49.9)	
No	5,383 (50.6)	307 (43.2)	99 (55.7)	1,043 (54.6)	3,934 (50.1)	
Muscular exercise						<0.001[a]
Never	7,521 (71.0)	428 (60.5)	126 (68.8)	1,326 (71.0)	5,641 (72.1)	
1–2/wk	1,150 (11.7)	91 (13.8)	25 (14.0)	204 (10.9)	830 (11.6)	
≥3/wk	1,638 (17.4)	152 (25.6)	28 (17.2)	323 (18.1)	1,135 (16.3)	
Body mass index						<0.001[a]
Underweight	567 (5.5)	15 (1.9)	5 (2.1)	73 (3.8)	474 (6.4)	
Normal	4,485 (42.2)	208 (29.8)	58 (31.9)	617 (33.7)	3,602 (46.2)	
Overweight	2,063 (20.1)	132 (21.1)	38 (21.9)	428 (23.4)	1,465 (19.0)	
Obesity	3,194 (32.2)	316 (47.2)	78 (44.1)	735 (39.0)	2,065 (28.4)	
Hypertension						<0.001[a]
Yes	575 (5.3)	42 (5.7)	11 (5.5)	157 (7.8)	365 (4.6)	
No	9,734 (94.7)	629 (94.3)	168 (94.5)	1,696 (92.2)	7,241 (95.4)	
Diabetes mellitus						<0.001[a]
Yes	186 (1.8)	12 (1.6)	5 (2.7)	68 (3.6)	101 (1.3)	
No	10,123 (98.2)	659 (98.4)	174 (97.3)	1,785 (96.4)	7,505 (98.7)	

Values are presented as number (weighted %) or mean±standard error. Different alphabets indicate significant differences.

HTPs, heated tobacco products; CCs, combustible cigarettes.

[a]Statistical analysis by chi-square test (Rao-Scott χ^2 test). [b]Statistical analysis by general linear model analysis.

binge drinking was lowest among never-smokers and highest in the "current CCs only user" group. The "HTPs ever user" group showed the highest rate of physical activity, and the "current HTPs only user" group had the highest rate of muscle-strengthening exercises performed 3 or more times per week.

Regarding BMI, the "HTPs ever user" group had the highest obesity rate, while the never-smoker group had the lowest. The prevalence of hypertension and diabetes mellitus was highest in the "current CCs only user" group and lowest in the never-smoker group.

Serum lipid profiles according to smoking type

A general linear model analysis and chi-square test were conducted

to examine differences in serum lipid concentrations based on smoking type. The serum lipid profiles according to current smoking status are summarized in Table 2.

The mean TC level differed significantly by smoking type (P=0.001), with the highest average level observed in the "current HTPs only user" group. The proportion of individuals with "high" or "borderline" TC also showed significant differences (P=0.003), with the "current HTPs only user" group having the highest proportions of TC levels

above 240 mg/dL and between 200 mg/dL and 240 mg/dL.

The mean HDL-C level showed significant differences according to smoking type (P<0.001), with the lowest average level observed in the "current CCs only user" group. Similarly, the proportion of individuals with low HDL-C levels showed significant differences (P<0.001), with the highest proportion of low HDL-C observed in the "current CCs only user" group. While the mean HDL-C level did not show significant differences when analyzed by gender, the proportion of men with

Table 2. Serum lipid level according to smoking status

Variable	Total	Smoking status				P-value
		HTPs ever user	Current HTPs only user	Current CCs only user	Never smoker	
No. of patients	10,309	671	179	1,853	7,606	
Total cholesterol (mg/dL)	194.86±0.45	196.32±1.40[ab]	203.41±2.86[c]	196.41±1.12[b]	194.04±0.49[a]	0.001[a)]
<200	5,901 (57.7)	365 (55.5)	86 (46.3)	1,042 (56.0)	4,408 (58.7)	0.003[b)]
200–239	3,364 (32.5)	228 (33.4)	73 (41.8)	606 (32.2)	2,457 (32.2)	
≥240	1,044 (9.8)	78 (11.1)	20 (12.0)	205 (11.9)	741 (9.1)	
HDL cholesterol (mg/dL)						
Total	53.67±0.16	51.30±0.53[b]	50.94±0.98[ab]	49.38±0.32[a]	55.19±0.20[c]	<0.001[a)]
Normal	7,753 (76.2)	545 (81.8)	154 (86.4)	1,373 (75.5)	5,681 (75.6)	<0.001[b)]
Low	2,556 (23.8)	126 (18.2)	25 (13.6)	480 (24.5)	1,925 (24.4)	
Male	48.54±0.20	49.44±0.56	49.13±0.98	47.92±0.32	48.72±0.29	0.080[a)]
Normal	3,105 (79.5)	446 (82.4)	123 (89.1)	1,140 (76.7)	1,396 (80.2)	0.004[b)]
Low	840 (20.5)	95 (17.6)	14 (10.9)	380 (23.3)	351 (19.8)	
Female	57.87±0.21	61.48±1.37	58.30±2.10	57.25±0.89	57.82±0.22	0.054[a)]
Normal	4,648 (73.5)	99 (78.5)	31 (75.4)	233 (68.9)	4,285 (73.7)	0.243[b)]
Low	1,716 (26.5)	31 (21.5)	11 (24.6)	100 (31.1)	1,574 (26.3)	
LDL cholesterol (mg/dL)	118.07±0.40	118.35±1.20[a]	124.93±2.53[b]	117.08±1.03[a]	118.13±0.43[a]	0.043[a)]
<130	6,887 (67.0)	437 (66.2)	105 (54.6)	1,240 (66.5)	5,105 (67.5)	0.017[b)]
130–159	2,488 (24.1)	162 (22.9)	54 (33.2)	439 (23.8)	1,833 (24.0)	
≥160	934 (8.9)	72 (10.9)	20 (12.2)	174 (9.6)	668 (8.4)	
Triglyceride (mg/dL)	124.08±1.31	148.97±5.89[b]	151.15±7.55[b]	171.76±4.03[c]	107.51±1.15[a]	<0.001[a)]
<150	7,879 (75.8)	438 (65.8)	106 (59.9)	1,073 (58.4)	6,262 (82.1)	<0.001[b)]
150–199	1,159 (11.4)	110 (15.9)	35 (21.2)	297 (15.4)	717 (9.5)	
≥200	1,271 (12.8)	123 (18.3)	38 (18.9)	483 (26.1)	627 (8.4)	

Values are presented as mean±standard error or number (weighted %). Different alphabets indicate significant differences.
HTPs, heated tobacco products; CCs, combustible cigarettes; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a)]Statistical analysis by general linear model analysis. [b)]Statistical analysis by chi-square test (Rao-Scott χ^2 test).

Table 3. Adjusted odds ratios for the impact of smoking status on serum lipid levels

Dependent variable	Smoking status			
	Never smoker	HTPs ever user	Current HTPs only user	Current CCs only user
Total cholesterol (Ref: <200 mg/dL)				
200–239	1.00	1.08 (0.87–1.34)	1.37 (0.93–2.02)	0.90 (0.76–1.06)
≥240	1.00	1.40 (1.03–1.92)	1.48 (0.84–2.59)	1.27 (0.96–1.67)
HDL cholesterol (Ref: normal)				
Low	1.00	0.98 (0.76–1.25)	0.62 (0.36–1.06)	1.52 (1.28–1.80)
LDL cholesterol (Ref: <130 mg/dL)				
130–159	1.00	0.98 (0.79–1.22)	1.55 (1.05–2.28)	0.95 (0.80–1.12)
≥160	1.00	1.44 (1.04–2.00)	1.71 (1.01–2.89)	1.13 (0.86–1.48)
Triglyceride (Ref: <150 mg/dL)				
150–199	1.00	1.18 (0.89–1.57)	1.65 (0.99–2.73)	1.26 (1.02–1.57)
≥200	1.00	1.29 (0.97–1.71)	1.34 (0.86–2.09)	2.08 (1.69–2.58)

Values are presented as adjusted odds ratio (95% confidence interval). Adjusted for sex, age, education, household income, living alone, high-risk drinking, physical activity, muscular exercise, body mass index, hypertension, and diabetes mellitus. Statistical analysis by logistic regression analysis.
HTPs, heated tobacco products; CCs, combustible cigarettes; Ref, reference; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
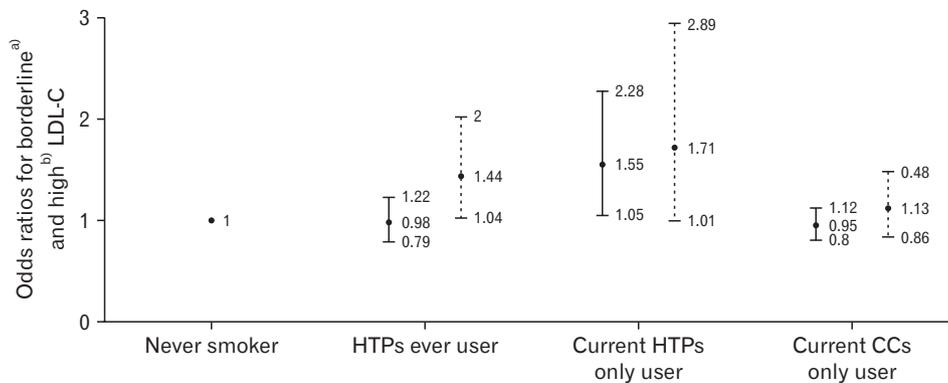
Figure 1. Odds ratios for borderline and high low-density lipoprotein cholesterol (LDL-C) compared to the never-smoker group. Statistical analysis by logistic regression analysis. HTPs, heated tobacco products; CCs, combustible cigarettes. [a]Solid lines, LDL-C from 130 to 159 mg/dL. [b]Dotted lines, LDL-C ≥160 mg/dL.

low HDL-C levels did vary significantly by smoking type (P=0.004), with the highest proportion also seen in the "current CCs only user" group.

The mean LDL-C levels showed significant differences across smoking types (P=0.043), with relatively higher levels observed in the "current HTPs only user" group. The proportion of individuals with "high" or "borderline" LDL-C levels also showed significant differences (P=0.017), with the "current HTPs only user" group having the highest proportions of LDL-C levels above 160 mg/dL and between 130 and 160 mg/dL.

The mean TGs levels also showed significant differences by smoking type (P<0.001), with the highest levels observed in the "current CCs only user" group. The proportion of individuals with "high" or "borderline" TGs demonstrated significant differences (P<0.001), with the highest proportion of TGs above 200 mg/dL found in the "current CCs only user" group, while the highest proportion of TGs between 150 and 200 mg/dL was observed in the "current HTPs only user" group.

Associations between smoking type and serum lipid profiles

The associations between smoking type and serum lipid profiles are summarized in Table 3. Logistic regression analysis was conducted to assess the effect of smoking type on serum lipid profiles. The analysis controlled for the effects of gender, age, education level, household income, living arrangement (living alone or not), binge drinking frequency, physical activity, muscle-strengthening exercises, BMI, hypertension, and diabetes mellitus, to isolate the direct effect of smoking type on serum lipid concentrations.

First, the effect of smoking type on TC levels was examined. Compared to never-smokers, the "HTPs ever user" group had a significantly higher likelihood of having "high" TC levels above 240 mg/dL (odds ratio [OR], 1.40; 95% confidence interval [CI], 1.03–1.92).

Next, the effect of smoking type on HDL-C levels was analyzed. The results indicated that compared to never-smokers, the "current CCs only user" group had a significantly higher chance of having "low" HDL-C levels (OR, 1.52; 95% CI, 1.28–1.80).

The effect of smoking type on LDL-C levels was also examined. Compared to never-smokers, the "current HTPs only user" group had a significantly greater likelihood of having "borderline" LDL-C levels

between 130 mg/dL and 160 mg/dL (OR, 1.55; 95% CI, 1.05–2.28) (Figure 1). Additionally, the "HTPs ever user" group (OR, 1.44; 95% CI, 1.04–2.00) and the "current HTPs only user" group (OR, 1.71; 95% CI, 1.01–2.89) showed a significantly higher probability of having "high" LDL-C levels above 160 mg/dL. This suggests that "current HTPs only users" are more likely to have elevated LDL-C levels compared to "never smokers."

Finally, the effect of smoking type on TG levels was investigated. Compared to never-smokers, the "current CCs only user" group had a significantly higher likelihood of having "borderline" TG levels between 150 mg/dL and 200 mg/dL (OR, 1.26; 95% CI, 1.02–1.57). The likelihood of having "high" TG levels above 200 mg/dL was also significantly greater in the "current CCs only user" group (OR, 2.08; 95% CI, 1.69–2.58).

Discussion

Various findings have been reported on the relationship between LDL-C levels and smoking CCs. In the study by Scherer [14], which analyzed 23 studies on the correlation between CC smoking and LDL-C levels, it was found that the LDL-C levels of CC smokers were about 4% higher than those of non-smokers across a total of 50,000 participants. Moreover, only four out of 17 studies showed significant differences in LDL-C levels between smokers and non-smokers. Studies comparing current smokers with ex-smokers found no significant differences in LDL-C levels. Among the seven studies comparing ex-smokers with never-smokers, only one reported higher LDL-C levels in the ex-smokers. This suggests that it can take a relatively long time—approximately 2 years on average—for LDL-C levels to return to those seen in non-smokers after quitting smoking. In the present study, the "HTPs only user" group included individuals who had transitioned from smoking CCs to using HTPs. Therefore, it is possible to speculate that current HTP use, combined with a history of CC smoking, may have jointly influenced LDL-C levels.

Ongoing research has investigated how CC smoking induces dyslipidemia [10,15,16]. Nicotine from cigarettes acts on the adrenal cortex, increasing the secretion of catecholamines, which leads to the breakdown of fat cells and an elevation of free fatty acids in the blood. This

process promotes the production of very LDL-C (VLDL-C) and TGs in the liver. HDL-C levels change inversely with VLDL-C concentrations and are known to decrease rapidly after smoking begins. These changes are believed to influence the lipid profile of smokers, including LDL-C levels.

Previous studies on the serum lipid levels of users of HTPs are still limited, particularly those examining the impact of HTP smoking on LDL-C levels. Notably, many of these studies have been led by HTP manufacturers. In a study by Haziza et al. [17], conducted by "IQOS" manufacturer PMI, biomarkers were analyzed for three groups: those who switched from smoking CCs to HTPs, those who continued smoking CCs, and those who quit smoking altogether. Although the P-value was greater than 0.05, LDL-C, HDL-C, apolipoprotein A1, apolipoprotein B, and TC all showed a trend of improvement in the group that switched from CCs to HTPs. In the study of Sakaguchi et al. [18], funded by Japan Tobacco Inc., a cross-sectional analysis of HTP users was performed, and no significant differences in LDL-C levels were found when compared to CC users and non-smokers. However, exclusive HTP users had higher HDL-C concentrations than CC smokers. Additionally, a randomized trial sponsored by PMI showed that CC smokers who switched to HTPs had higher HDL-C concentrations at 6 months compared to those who continued smoking CCs [19]. In an independent, large population-based study in Japan, exclusive HTP users had lower HDL-C concentrations than never-smokers, though their HDL-C levels were still higher than those of exclusive CC smokers [20].

Since the introduction of HTPs, several studies have reported on their harmful components. A study by Uchiyama et al. [21] concluded that the total gaseous particulate matter emitted per cigarette did not differ significantly between CCs and HTPs. Nicotine emissions were measured at 1,900 μg per CC, 1,200 μg per IQOS, and 510 μg per glo. In a study by Bekki et al. [22], the amount of nicotine emitted from the filler and mainstream smoke of IQOS was found to be almost equivalent to that of CCs. However, tobacco-specific nitrosamines (TSNAs) were emitted at one-fifth the level of CCs, and carbon monoxide emissions were one-hundredth of those produced by CCs.

Upadhyay et al. [23] compared various studies that analyzed the harmful components of HTPs. Based on emissions from CCs, they found that nicotine and tar from HTPs amounted to approximately 70% of that from CCs, ammonia and formaldehyde were around 30%, reactive oxygen species were about 25%, TSNAs and acrolein were around 10%, and carbon monoxide was less than 5%. Aromatic amines, known carcinogens, were not detected in HTP smoke. PMI has also submitted data indicating that fewer harmful substances are emitted from IQOS compared to CCs.

However, according to a study by St. Helen et al. [24], pointed out that the data on IQOS provided by PMI included only 40 of the 93 HPHCs identified by the US Food and Drug Administration. They argued that 15 of the HPHCs not analyzed by the manufacturer are produced at more than double the levels in CCs, and seven of these are generated at more than 10 times the amount.

One consideration when comparing harmful emissions from HTPs is that HTP sticks are about half the size of CC sticks [23]. Therefore, even if the amount of nicotine and other harmful substances per HTP stick is slightly lower than that of CCs, smokers might increase their consumption of HTPs per session to meet their usual nicotine intake. Additionally, it cannot be completely ruled out that nicotine and other harmful substances in HTPs, which are not present in CCs, may have influenced smokers' LDL-C levels.

This study has several limitations. First, as a cross-sectional study using raw data from the National Health and Nutrition Examination Survey, it cannot establish a causal relationship between HTP smoking and increased serum LDL-C concentration. Future research should focus on larger-scale, long-term epidemiological and mechanistic studies. Second, the study did not quantitatively assess the dose-response relationship or cumulative effect of HTP smoking on serum LDL-C levels, as detailed surveys on smoking behavior were not conducted for HTP users. Thus, the amount and duration of HTP use were not considered. Reports suggest that increased smoking among CC smokers exacerbates dyslipidemia, including high LDL-C [15]. Therefore, future studies should take into account various factors in smoking behavior, such as the amount smoked and the total duration of smoking, for HTP users. Third, recall bias may have occurred since smoking habits were self-reported through questionnaires. Using biological markers, such as salivary or urinary cotinine, to verify smoking type could yield more objective results regarding the effects of smoking in HTP users. Finally, the statistical significance of the results may be limited by the relatively small number of HTP users in the study. However, as mentioned in the introduction, the number of HTP users in Korea is steadily increasing, and the market is rapidly expanding. Therefore, research on the health effects of HTPs is essential for public health promotion and disease prevention.

In conclusion, current exclusive HTP smoking is associated with both borderline and high serum LDL-C levels. To our knowledge, no previous studies have addressed this issue. Further research should explore whether long-term HTP use has harmful effects on users' serum lipid profiles. Additionally, the health risks associated with dual and triple tobacco use should be investigated in larger populations.

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