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Toffol, Elena

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GYNECOLOGY

Metabolomics profile of 5649 users and nonusers of hormonal intrauterine devices in Finland

Elena Toffol, MD, PhD; Oskari Heikinheimo, MD, PhD; Pekka Jousilahti, MD, PhD; Anna But, PhD; Anni Joensuu, MSc; Antti Latvala, PhD; Timo Partonen, MD, PhD; Iris Erlund, PhD; Jari Haukka, PhD

BACKGROUND: Use of hormonal intrauterine devices has grown during the last decades. Although hormonal intrauterine devices act mostly via local effects on the uterus, measurable concentrations of levonorgestrel are absorbed into the systemic circulation. The possible metabolic changes and large-scale biomarker profiles associated with hormonal intrauterine devices have not yet been studied in detail.

OBJECTIVE: To examine through the metabolomics approach the metabolic profile of patients using hormonal intrauterine devices and how this metabolic profile is affected by duration and discontinuation of use.

STUDY DESIGN: The study consisted of cross-sectional analyses of 5 population-based surveys (FINRISK and FinHealth studies), spanning from 1997 to 2017. All fertile-aged participants (18−49 years) in the surveys with available information on hormonal contraceptive use and metabolomics data (n=5649) were included in the study. Altogether, 211 metabolic measures of users of hormonal intrauterine devices (n=1006) were compared with those of nonusers of hormonal contraception (n=4643) via multivariable linear regression models. To allow comparison across multiple measures, association magnitudes were reported in standard deviation units of difference in biomarker concentration compared with the reference group.

RESULTS: After adjustment for covariates, levels of 141 metabolites differed in current users of hormonal intrauterine devices compared with nonusers of hormonal contraception (median difference in biomarker concentration, 0.09 standard deviation): lower levels of particle concentration of larger lipoprotein subclasses, triglycerides, cholesterol and derivatives, apolipoproteins A and B, fatty acids, glycoprotein acetyls, and aromatic amino acids. The metabolic pattern of hormonal intrauterine device use did not change according to duration of use. When comparing previous users and never-users of hormonal intrauterine devices, no significant metabolic differences were observed.

CONCLUSION: The use of hormonal intrauterine devices was associated with several moderate metabolic changes previously associated with reduced arterial cardiometabolic risk. The metabolic effects were independent of duration of use of the hormonal intrauterine devices. Moreover, the metabolic profiles were similar after discontinuation of hormonal intrauterine device use and in never-users.

Key words: discontinuation of use, duration of use, fertile-aged, hormonal intrauterine devices, metabolic changes, metabolites

Introduction

The 52-mg levonorgestrel (LNG) intrauterine device (IUD) is a highly effective reversible contraceptive with an approved duration of use of 6 years. It was first marketed in the Nordic countries in early 1990s, and in the United States in 2000. Although primarily used by the older fertile age group, in the Nordic countries approximately 20% of women aged 15 to 49 years used hormonal IUDs in the period from 2010 to 2013,[1] and their use is increasing globally. Many users opt to continue use with subsequent devices. Because of their high efficacy, hormonal IUDs and other long-acting reversible contraceptives are being promoted as first-line contraceptives to all subjects by international guidelines on contraception.[2] The contraceptive mechanism of action of hormonal IUDs involves mainly local effects on cervical mucus and the endometrium.[3] Nevertheless, measurable concentrations of LNG are absorbed into the systemic circulation, possibly leading to systemic effects.[4] Thus, an increasing number of fertile-aged individuals are exposed for several years to this 19-nortestosterone derivative. Therefore, the possible long-term metabolic effects of hormonal IUDs are of great clinical interest.

Contrary to the use of combined oral contraceptives (COCs) containing other nonandrogenic progestins, the use of COCs containing LNG is associated with changes in lipid concentrations, with apparently no effect on body mass index (BMI), insulin resistance, or fasting plasma glucose levels.[5] Conversely, progestin-only contraceptives, including the LNG implants and intrauterine systems, seem to have a safer metabolic profile.[6,7] The metabolic effects of hormonal IUDs have previously been studied in postmenopause in combination with estrogen replacement therapy, and in fertile-aged patients diagnosed with endometriosis and polycystic ovary syndrome (PCOS).[8,9] The 52-mg LNG IUDs have also been compared with copper 380 mm^2 IUDs among fertile-aged individuals in need of contraception.[10] According to these studies, the use of hormonal IUDs is not associated with increased risk of cardiovascular accidents.[7−9,11−15]

However, the possible metabolic changes and large-scale biomarker profiles associated with the use of hormonal IUDs have not been studied in detail to

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AJOG at a Glance

Why was this study conducted?

The use of hormonal intrauterine devices is increasing globally, and many users opt for subsequent devices. Thus, an increasing number of fertile-aged individuals are exposed for several years to levonorgestrel, calling for the assessment of possibly related metabolic changes and large-scale biomarker profiles.

Key findings

After adjustment for covariates, levels of 141 metabolites differed between current users of hormonal intrauterine devices and nonusers of hormonal contraception. The metabolic patterns were similar irrespective of duration of use; most of the metabolic alterations were not evident in previous users.

What does this add to what is known?

The use of hormonal intrauterine devices is associated with many moderate metabolic changes, suggestive of reduced arterial cardiometabolic risk. The associations seemed to be mostly independent of duration of use and to not persist after discontinuation of use.

date. To the best of our knowledge, only 1 previous study used the metabolomics technique to examine the metabolic biomarkers of 52-mg LNG IUD use. Wang et al[16] analyzed data of 464 users of 52-mg LNG IUD from 3 surveys conducted in Finland between 1996 and 2001, and found only few weak (−0.2 to −0.1 standard deviation [SD]) associations between 52-mg LNG IUD use and any metabolic biomarkers in a cross-sectional setting, and no associations in a longitudinal setting. Even scarcer are data on the duration of possible metabolic effects and biomarker alterations associated with hormonal IUD use.

Thus, the aim of this study was to examine the associations of hormonal IUD use with 211 metabolites in a large sample of older fertile-aged users and nonusers in Finland. An additional aim was to investigate whether the possible metabolic correlates of hormonal IUD are related to the duration of use and whether they persist after its discontinuation.

Materials and Methods

The material for this study was selected from 5 population-based surveys conducted in Finland between 1997 and 2017, namely the FINRISK 1997, 2002, 2007, and 2012,[17] and the FinHealth 2017[18] studies. The population for each FINRISK survey consisted of a new independent simple random sample of individuals drawn from the Finnish Population Information System, stratified by area, sex, and 10-year age group.[17] Population for the FinHealth 2017 study was sampled following a stratified 1- and 2-stage sampling design. To this end, mainland Finland was divided into 20 strata, and for each stratum a sample proportional in size to the corresponding population size was selected.[18] Thus, the target population for each survey consisted of a representative random sample of the Finnish population aged 25 to 74 years (FINRISK) or 18 to 99 years (FinHealth 2017). All the surveys consisted of self-administered questionnaires and a health examination including clinical measurements and blood sampling. The surveys were approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District. All participants gave written informed consent.

Study population

The population of this study was a convenience sample selected among all respondents, inclusive of all fertile-aged (18−49 years) participants with available (self-reported) information on their current and past use of hormonal contraceptives (HCs), and metabolomics data obtained from serum samples drawn during the health examination.

In each survey, we applied the following exclusion criteria to the initial available population: current pregnancy, menopause ("Do you still menstruate?" answered with "No, I last menstruated xxx years ago."), current use of hormonal replacement therapy, hysterectomy, and current use of oral contraceptive pills (or of vaginal ring, transdermal patch, or other HC—information available only in FinHealth 2017), resulting in a final population of 5649 individuals with available metabolomics data (1006 currently using a hormonal IUD, and 4643 HC nonusers). Detailed sample size and background information for each survey is reported in Supplemental Table 1 and Supplemental Figure 1.

Hormonal contraception

Information on current and previous use of HCs (pills and hormonal IUD) and its duration was obtained through questions in the self-administered questionnaires. All surveys additionally inquired into current and past use of nonhormonal IUDs; the FinHealth 2017 study also included information on the use of contraceptive vaginal rings, patches, or other HCs.[19,20] The 52-mg LNG IUD was the only hormonal IUD commercially available in Finland until 2013; the 13.5-mg LNG IUD has been available since February 2013, and the 19.5-mg LNG IUD since November 2016. The typical maximum duration of use of 52-mg and 19.5-mg LNG IUDs in Finland is 5 years (with the possibility, since late 2015, of extension of up to 7 years for the 52-mg LNG IUD, as recommended by the Finnish national guideline on contraception).[21] The maximum duration of use of 13.5-mg LNG IUD is 3 years.

Covariates

In addition to age, covariates obtained from the self-administered questionnaires and clinical measurements included the following: season of sampling; frequency of alcohol use (once a month or more, less than once a month, never/quit); smoking status (currently smoking, stopped smoking, never smoked); physical activity (as frequency of leisure time exercise: ≥4 times/week;

1−3 times/week; <1 time/week or disability); current use (during the past 7 days) of medications (painkillers, antibiotics, anticoagulants, sleeping pills, tranquilizers, antidepressants, antihistamines, acetylsalicylic acid for prevention of myocardial infarction, asthma medications, cholesterol medication, insulin and/or tablets for diabetes mellitus); history (ever or during past year) of diseases (asthma, hypertension, increased serum cholesterol, myocardial infarction, cardiac insufficiency, coronary heart disease, cerebrovascular accidents, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus, latent diabetes mellitus, depression, other psychological illnesses, rheumatoid arthritis, cancer), and BMI based on the measured height and weight.

Metabolomics measures

In each survey, the metabolomics measures were obtained from blood samples drawn during the health examination, after 4-hour fasting. The samples were collected and centrifuged at the field survey sites and then transported to the quality-controlled central laboratory, where the serum samples were stored at −70°C or colder. Serum sections were analyzed through a high-throughput serum nuclear magnetic resonance (NMR) metabolomics platform (^{1}H NMR Spectroscopy, Nightingale Health, Helsinki, Finland). Biomarkers were quantified independently for each serum sample. Nightingale's biomarker analysis technology applies a single experimental setup, and spectral information is converted to absolute concentrations (in molar units) of the metabolic measures. The platform allows the simultaneous quantification of 250 metabolic biomarkers per sample, including 12 lipid measures of 14 lipoprotein subclasses (6 very-low-density lipoproteins [VLDLs], 4 high-density lipoproteins [HDLs], 3 large-density lipoproteins [LDLs], intermediate-density lipoproteins [IDLs]), and other detailed molecular information on serum lipids (eg, sphingomyelin, fatty acids, etc.) or low-molecular-weight metabolites (eg, amino acids). An additional set of metabolite ratios is also computed.[22,23]

Statistical analyses

The analyses were first stratified by survey, and then conducted in the combined population obtained by pooling together on common variables the 5 datasets. After preliminary inspections of the metabolomics data in each cohort, metabolites with >100 missing observations were excluded from the analyses, resulting in a total of 211 metabolic measures; metabolic measures with value "zero" were replaced with 0.25 * (the minimum observed value for that metabolite), and after log transformation, remaining missing data were imputed through random forest imputation.[24]

Subsequent analyses were conducted using linear regression models, with each metabolic measure as the outcome variable, and use of a hormonal IUD (vs current nonuse of any HC) as the predictor of interest using the "ggforestplot" R-package.[25] Three models were fitted: Model 1, controlled for age, BMI, and study cohort; Model 2, which was Model 1 further controlled for history of diseases and medication use; Model 3, which was Model 1 further adjusted for alcohol use and smoking. Model 1 was repeated after stratification by age group. Moreover, because of the lack of comparable variables of physical activity in the FINRISK and FinHealth cohorts, Model 3 was repeated in the pooled FINRISK dataset only, with further inclusion of physical activity as an additional covariate (Supplemental Figure 2). Covariates for the models were selected a priori on the basis of the current knowledge on metabolic risk factors and HC use. To allow comparison across multiple measures, association magnitudes were reported in SD units of difference in biomarker concentration compared with the reference group. Results of analyses conducted separately in each dataset are reported in Supplemental Table 1 and Supplemental Figures 3 to 5.

To further examine whether the possible associations of hormonal IUD use with specific metabolic patterns are detectable after discontinuation of use, we conducted additional linear regression models (adjusted for age, BMI, and study cohort) comparing the associations of current and previous use of hormonal IUDs with all the metabolic measures, with never-users of hormonal IUDs as the reference category.

Moreover, to test the possible effect of duration of use on the metabolic profiles of hormonal IUDs, we performed a linear regression model (Model 1) in the group of current users only, comparing intermediate-term (1−5 years) and long-term (>5 years) use of hormonal IUDs with short-term use (up to 1 year).

To take into account the multiple testing, the false-discovery rate procedure was applied.

All the analyses were performed with R software, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).[26]

Results

The baseline characteristics of the 5649 participants with available information on their current hormonal IUD use and metabolomics data are reported in the Table. Altogether, 1006 individuals (17.8%) were using a hormonal IUD at the time of the surveys; they were older than those not using any HC (mean±SD age, 40.4±5.9 vs 37.6±6.9). In addition, they were more likely to use alcohol, to not exercise regularly, to have a chronic disease, and to have used a medication during the previous week.

In linear regression analyses adjusted for age, BMI, and study cohort (Model 1), 141 of the 211 metabolic measures differed between hormonal IUD users and nonusers of HCs (median difference in biomarker concentration, 0.088 SD), with the main exceptions of glycolysis-related metabolites, amino acids (except for aromatic amino acids), fatty acid ratios, and to a certain extent, the proportions of lipids in lipoproteins (Figure 1). The associations were mostly driven by the oldest age group (40−49 years, n=2584), whereas they were not significant in the young

TABLE
Background characteristics of the study population

Characteristics	Hormonal IUD users n=1006 N (%)/mean (SD)	Hormonal contraception nonusers n=4643 N (%)/mean (SD)	*P* value
Age (range: 18–49 y)	40.4 (5.9)	37.6 (6.9)	<.0001
Age group			<.001
18–29 y	52 (5.2%)	754 (16.2%)	
30–39 y	354 (35.2%)	1905 (41.0%)	
40–49 y	600 (59.6%)	1984 (42.7%)	
BMI kg/m^2	25.7 (5.0)	25.4 (5.1)	.064
BMI category			.402
Underweight (BMI <18.5)	10 (1.0%)	81 (1.8%)	
Normal (BMI: 18.5–24.9)	544 (54.2%)	2535 (54.6%)	
Preobesity (BMI: 25–29.9)	274 (27.3%)	1248 (26.9%)	
Obesity class I (BMI: 30–34.9)	107 (10.7%)	460 (9.9%)	
Obesity class II (BMI: 35–39.9)	41 (4.1%)	164 (3.5%)	
Obesity class III (BMI >39.9)	27 (2.7%)	154 (3.3%)	
Season of sampling			.092
Dec–Feb	504 (50.1%)	2465 (53.1%)	
March–May	502 (49.9%)	2178 (46.9%)	
Alcohol use			<.0001
Once/month or more	667 (66.4%)	2704 (58.4%)	
Less than once a month	292 (29.1%)	1472 (31.8%)	
No/quit	45 (4.5%)	453 (9.8%)	
Smoking			.16
Smoking	231 (23.0%)	1092 (23.6%)	
Stopped	229 (22.8%)	930 (20.1%)	
Never smoked	545 (54.2%)	2609 (56.3%)	
Physical activity[a]			<.0001
≥4 times/wk	42 (5.6%)	308 (7.8%)	
1–3 times/wk	322 (42.5%)	2037 (51.4%)	
<1 time/wk or disability	393 (51.9%)	1620 (40.9%)	
Current use (past week) of any medication[b]	536 (55.0%)	2179 (48.3%)	.0002
Chronic disease (ever or past year)[c]	531 (55.6%)	2280 (51.1%)	.012

Pooled FINRISK and FinHealth data, n=5649.

BMI, body mass index; *IUD*, intrauterine device; *SD*, standard deviation.

[a] Data from FINRISK 1997, 2002, 2007, and 2012 only; [b] Painkillers, anticoagulants, sleeping pills, tranquilizers, antidepressants, hay fever medications, acetylsalicylic acid for preventing myocardial infarction, asthma medications, cholesterol medication, insulin and/or tablets for diabetes mellitus, antibiotics (not available in FINRISK 1997); [c] Asthma ever or in the past year; hypertension ever or in the past year; myocardial infarction, cerebrovascular accident, heightened cholesterol, diabetes mellitus (type 1, type 2, gestational diabetes mellitus), or latent diabetes mellitus ever; cardiac insufficiency, coronary heart disease or angina pectoris, depression, other psychological illness, rheumatoid arthritis, cancer, diabetes mellitus (only in FINRISK 2012), heightened cholesterol (only in FINRISK 2012), back diseases (only in FinHealth 2017), or other joint diseases (only in FinHealth 2017) in the past year.

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group (18–29 years, n=806) (Figure 2). The pattern of associations remained substantially unchanged after adjustment for history of disease and medication use (Model 2), and for lifestyle habits (Model 3) (Figure 1).

We further compared the metabolic profiles of current (n=1006) and previous (n=345) users of hormonal IUDs

FIGURE 1
Associations between hormonal IUDs and 211 metabolic measures

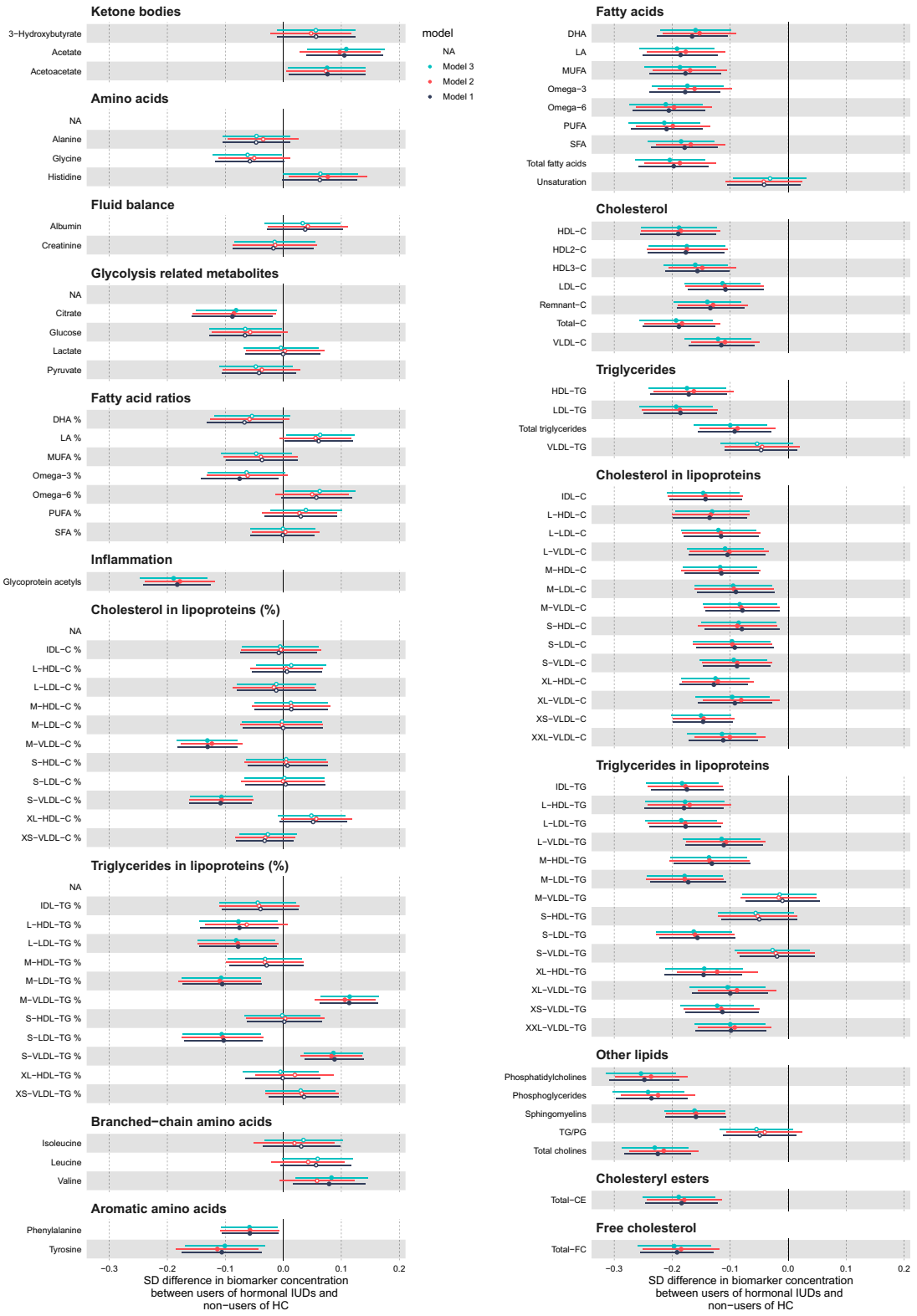

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FIGURE 1
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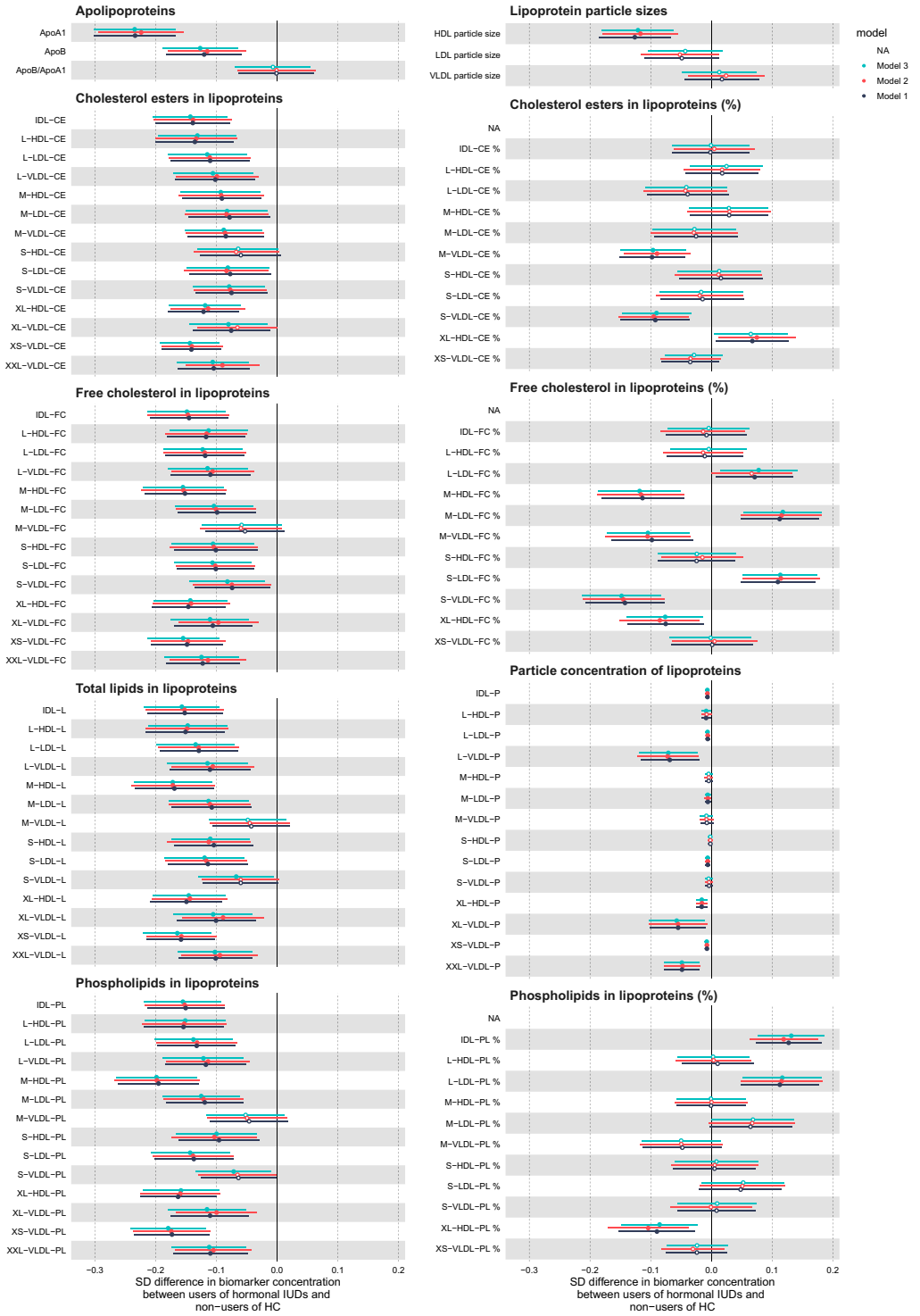

Analyses conducted in pooled FINRISK 1997, 2002, 2007, and 2012 and FinHealth 2017 surveys. Model 1 is adjusted for age, BMI, and study cohort; Model 2 is Model 1 further adjusted for history of disease and medication; Model 3 is Model 1 further adjusted for lifestyle habits (alcohol use and smoking). Results are in SD units of difference in metabolite concentrations; *bars* indicate 95% CI; reference category are nonusers of HCs. *Closed circles* indicate significant associations at *P* value adjusted for false discovery rate.

BMI, body mass index; *CI*, confidence interval; *HC*, hormonal contraceptive; *IUD*, intrauterine device; *SD*, standard deviation.

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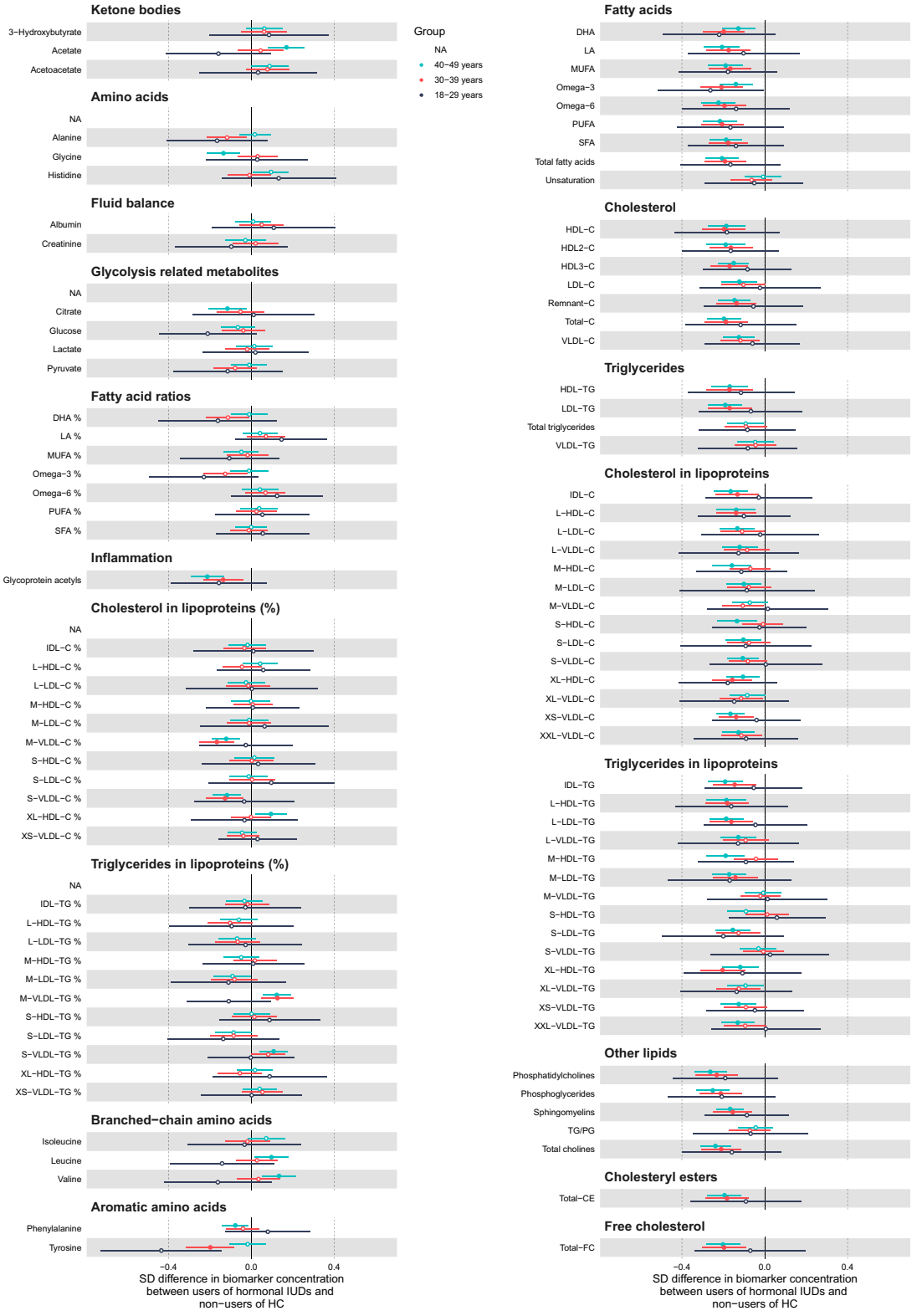
FIGURE 2
Age-stratified associations between hormonal IUDs and 211 metabolic measures



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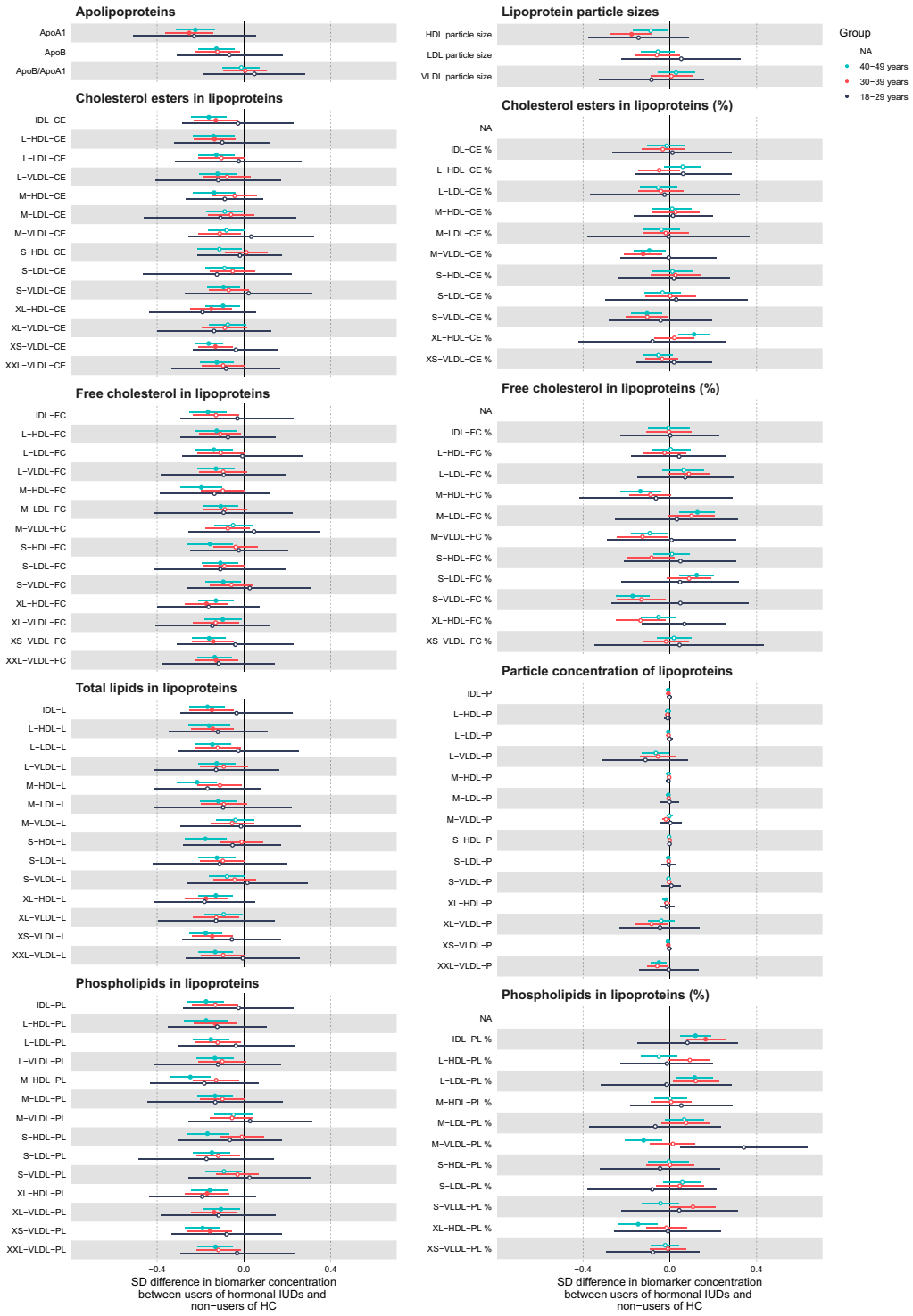

Analyses conducted in pooled FINRISK 1997, 2002, 2007, and 2012 and FinHealth 2017 surveys. Analyses are adjusted for age, BMI, and study cohort. Results are in SD units of difference in metabolite concentrations; *bars* indicate 95% CI; reference category are nonusers of HCs. *Closed circles* indicate significant associations at *P* value adjusted for false discovery rate.

BMI, body mass index; *CI*, confidence interval; *HC*, hormonal contraceptive; *IUD*, intrauterine device; *SD*, standard deviation.

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with those of never-users (n=4282) (Supplemental Table 2). A model adjusted for age, BMI, and study cohort substantially confirmed previous results of a significantly different metabolic profile in current users of hormonal IUDs compared with never-users (128/211 metabolites). Conversely, previous use of hormonal IUDs was not associated with a profile different from that of never-users (6/211 significant metabolites). Specifically, markers of lipid and fatty acid levels, lipoprotein composition, and ketone bodies seemed to differentiate current from previous users, being mostly significantly associated with current but not with former use (Figure 3).

To further examine whether the associations between the use of a hormonal IUD and metabolic profiles differ according to the duration of use, we conducted regression analyses in the subgroup of current users only, comparing the metabolic profile of intermediate (n=400) and long-term (n=377) use with that of short-term (n=170) use. No systematic differences were observed between the 3 groups (Figure 4). Although the findings did not reach significance levels, with longer duration of use there was a tendency toward higher levels of HDL3 cholesterol and cholesterol in XL-HDL, but lower levels of lipids in larger lipoproteins (XL-VLDL).

Comment

Principal findings

We found that a large number of metabolites differed between users of hormonal IUDs and nonusers of HCs. However, the magnitude of the associations was mostly from low to moderate, suggesting that the systemic effects of hormonal IUDs, if any, are of marginal size (median difference in biomarker concentration between users of a hormonal IUD and nonusers of HCs, 0.088 SD). Interestingly, the detected associations were suggestive of a protective profile in terms of, for example, arterial cardiovascular risk, with lower levels (compared with nonusers of HCs) of particle concentration of larger lipoprotein subclasses, and of triglycerides, cholesterol and derivatives (either as total or in lipoproteins), and other lipids, apolipoprotein (APO)-A1 and APO-B, aromatic amino acids, and the inflammation marker glycoprotein acetyls. Other key findings of our study are related to the duration of the possible metabolic effects of hormonal IUD use. Specifically, although the metabolic pattern of hormonal IUD use was similar irrespective of duration of use, most of the metabolic alterations seemed not to persist after discontinuation of hormonal IUD use, with previous users having an essentially similar profile to that of never-users.

Results in the context of what is known

Taken together, our findings indicate moderate, and mostly beneficial, metabolic modifications in older reproductive-aged users of hormonal IUDs compared with nonusers of HCs. These results are in line with previous evidence. Already in 1981, Nilsson et al[27] reported no difference in serum concentrations of HDL, total cholesterol, and triglycerides between users of the 52-mg LNG IUD and their nonuser controls. More recently, Ng et al[10] studied 92 healthy young subjects randomized to 18 months of either 52-mg LNG IUD or nonhormonal IUD, and found a reduction of total cholesterol in users of 52-mg LNG IUDs, and nonsignificant reductions in APO-A1 and APO-B. Conversely, HDL cholesterol decreased to significant levels after 6 months, but returned to baseline levels after 12 months in 52-mg LNG IUD users.[10] These observations were confirmed by a study of over 30,000 middle-aged subjects (37−44 years), reporting lower triglycerides and total, non-HDL, and HDL cholesterol in users of 52-mg LNG IUD than in nonusers of HCs. In addition, with longer durations of 52-mg LNG IUD use, the authors found increasing HDL cholesterol concentrations, but no associations with non-HDL cholesterol levels, triglyceride concentrations, or total or HDL cholesterol ratios.[28] Similarly, a population-based study reported similar levels of insulin, glucose, LDL cholesterol, triglycerides, and C-reactive protein in Finnish participants aged 31 years irrespective of 52-mg LNG IUD use or nonuse of any HCs.[29] Moreover, several studies of at-risk populations, such as patients with thrombophilia, cardiovascular disease, obesity, endometriosis, PCOS, or at risk for venous thromboembolism, supported the safety of 52-mg LNG IUD in terms of systemic effects, with minimal or beneficial metabolic changes, such as moderate, often nonsignificant weight gain, increase of fat mass, and changes in the lipid metabolism.[8,9,30−33]

Clinical implications

Most of the associations for the lipid panel were related to the absolute concentrations of lipids and lipids in lipoproteins, whereas associations with proportions of lipids in lipoproteins were less consistently significant (Figure 1). This suggests that the total amount, rather than the type of lipids, is mostly related to the use of hormonal IUDs. Specifically, levels of cholesterol and triglycerides in lipoproteins were especially lower (compared with nonusers) in the VLDL, IDL, and LDL subclasses, which are known to carry the highest arterial risk for cardiovascular events, and to a lesser extent in the HDL subclass. The associations of hormonal IUD use with lower levels of almost all types of lipids were consistently larger (although moderate) for IDL, XS-VLDL, S-LDL, L-LDL, XL-HDL, L-HDL, and M-HDL. This is especially important because it has been shown that the arterial cardiovascular risk of non-HDL cholesterol is mediated by both LDL (and especially the small dense LDL) and triglyceride-rich lipoproteins (such as IDL and VLDL).[34,35] Similarly, the observed decrease in absolute levels of all fatty acids is likely to reflect the overall lower lipid levels relative to HC nonusers, although no significant association with fatty acid balance was observed.

Another result suggestive of a healthier metabolic profile in older reproductive-aged hormonal IUD users were the reduced levels of the aromatic amino acids tyrosine and phenylalanine. Branched-chain and aromatic amino acids are

FIGURE 3
Associations between current and previous hormonal IUD and metabolic measures

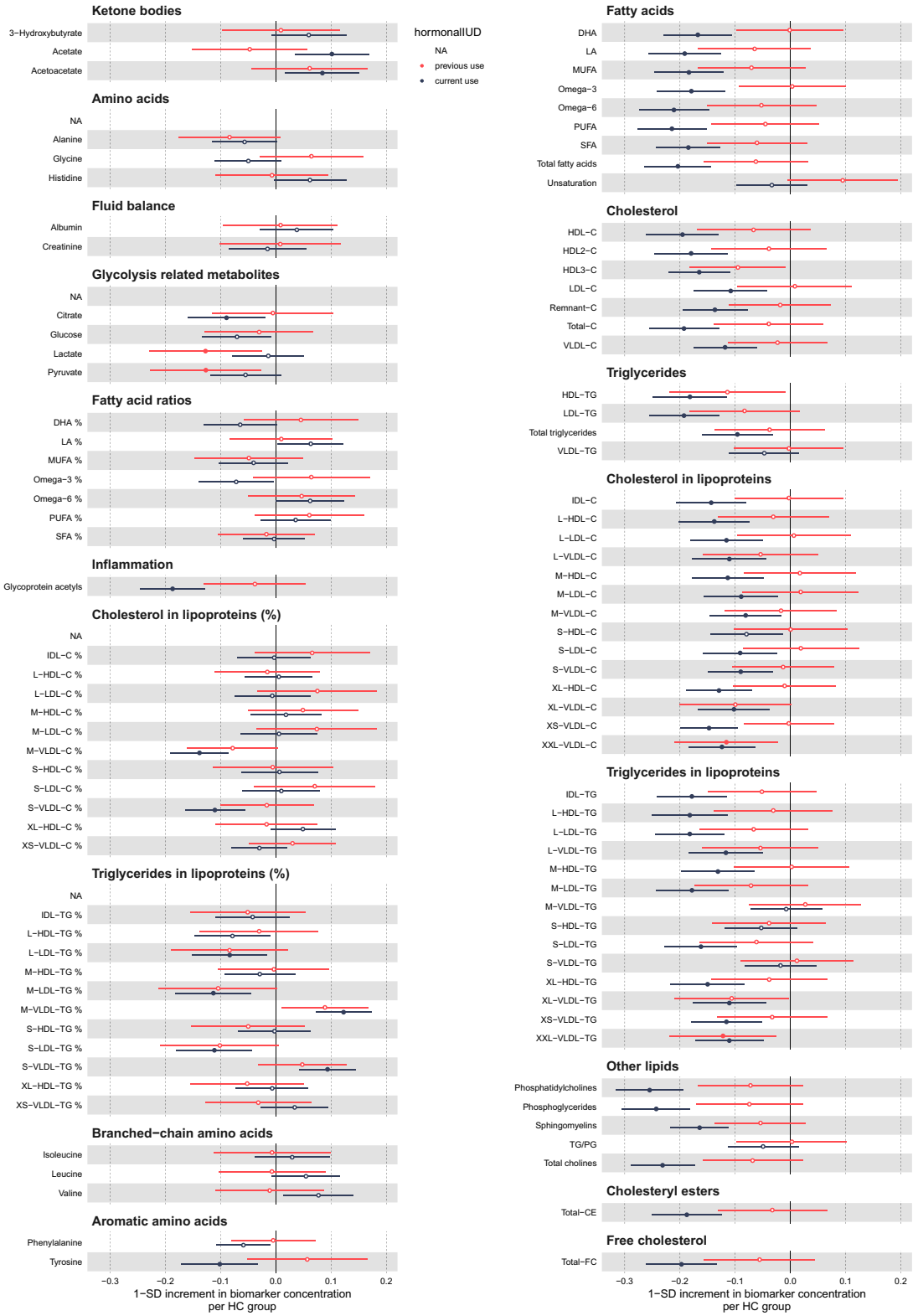

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FIGURE 3
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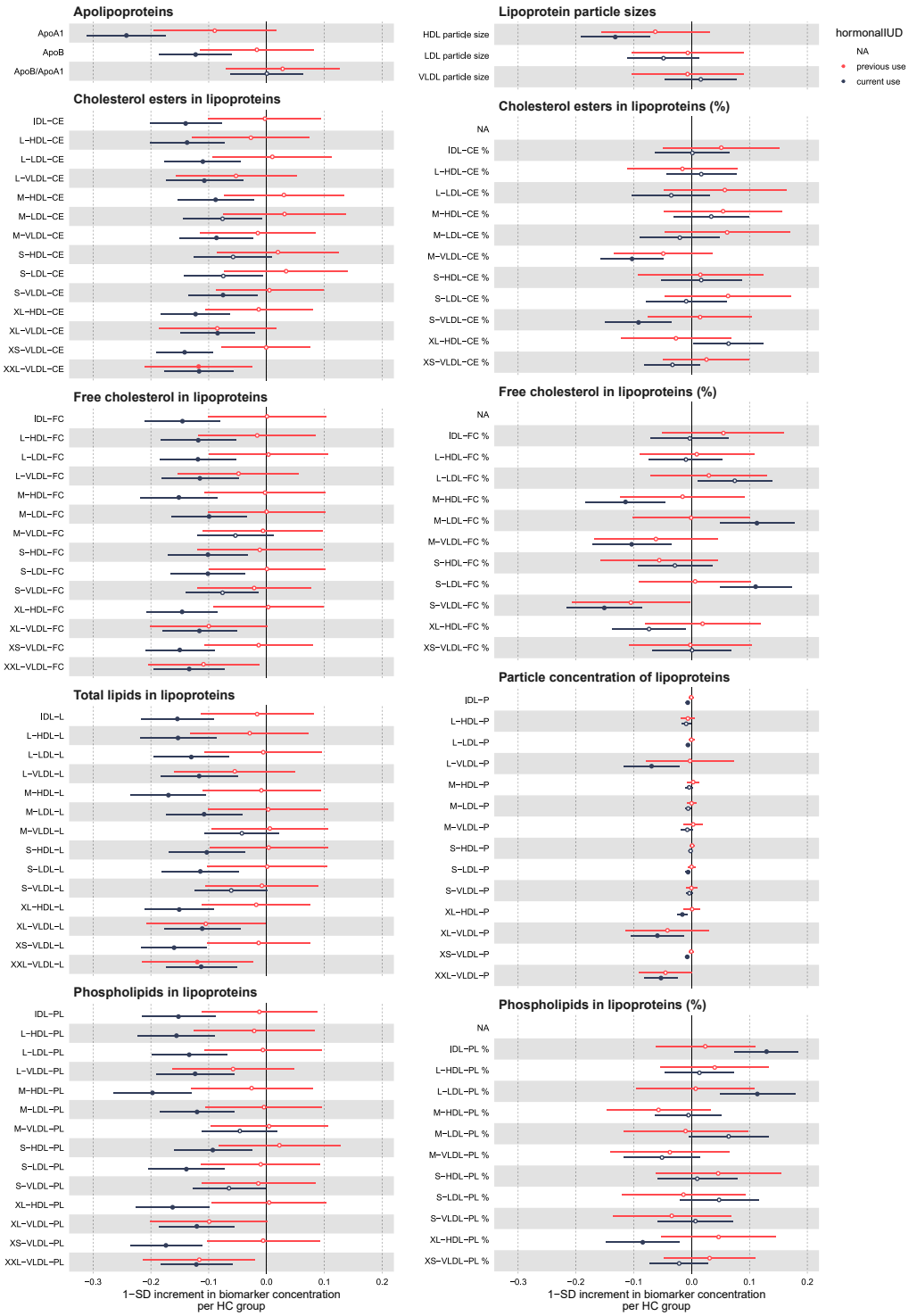

Analyses conducted in pooled FINRISK 1997, 2002, 2007, 2012, and FinHealth 2017 surveys. Analyses are adjusted for age, BMI, and study cohort. Results are in SD units of difference in metabolite concentrations; *bars* indicate 95% CI; reference category are never-users of hormonal IUDs. *Closed circles* indicate significant associations at *P* value adjusted for false discovery rate.

BMI, body mass index; *CI*, confidence interval; *IUD*, intrauterine device; *SD*, standard deviation.

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FIGURE 4
Associations between duration of hormonal IUD use and metabolic measures

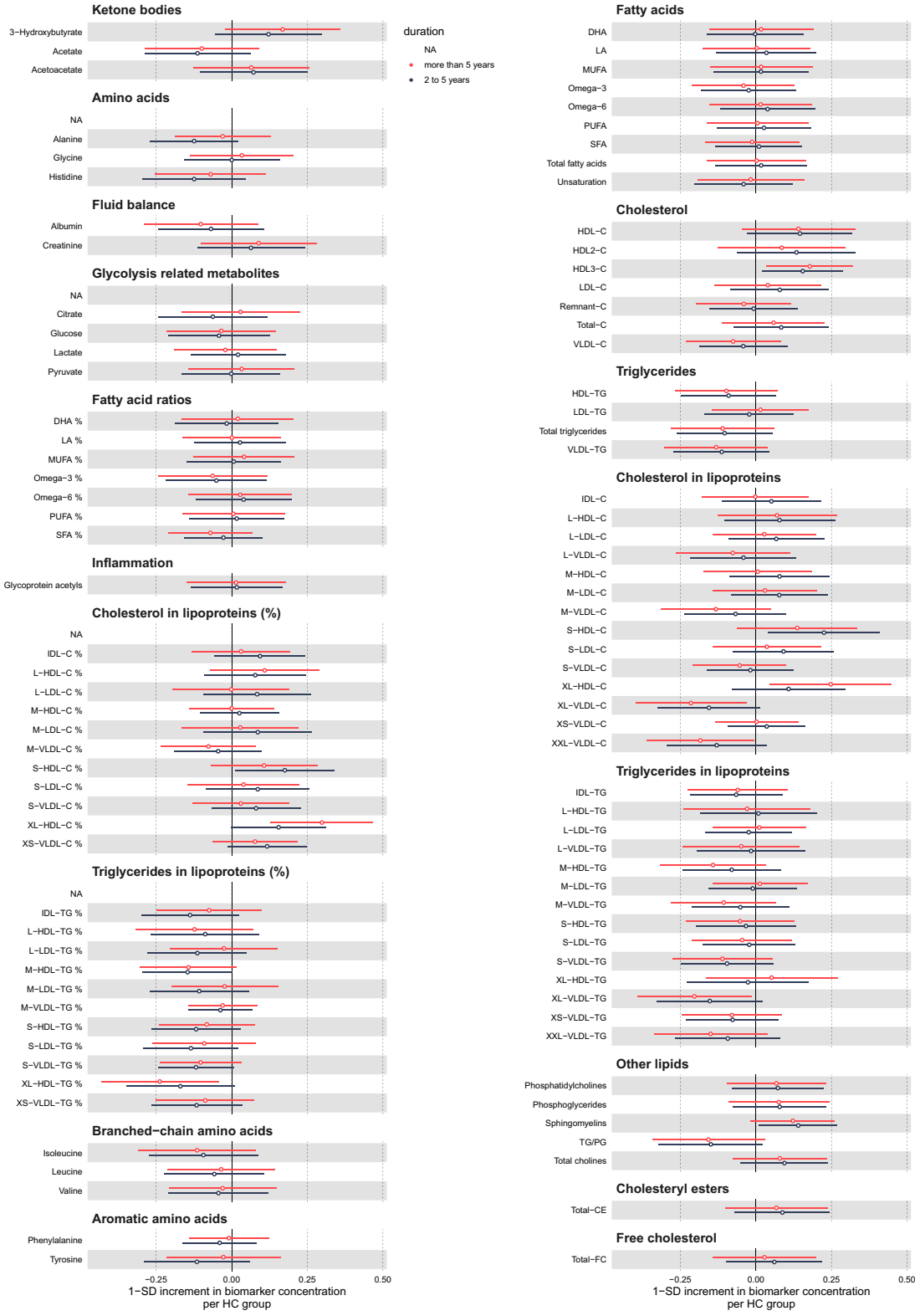

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FIGURE 4
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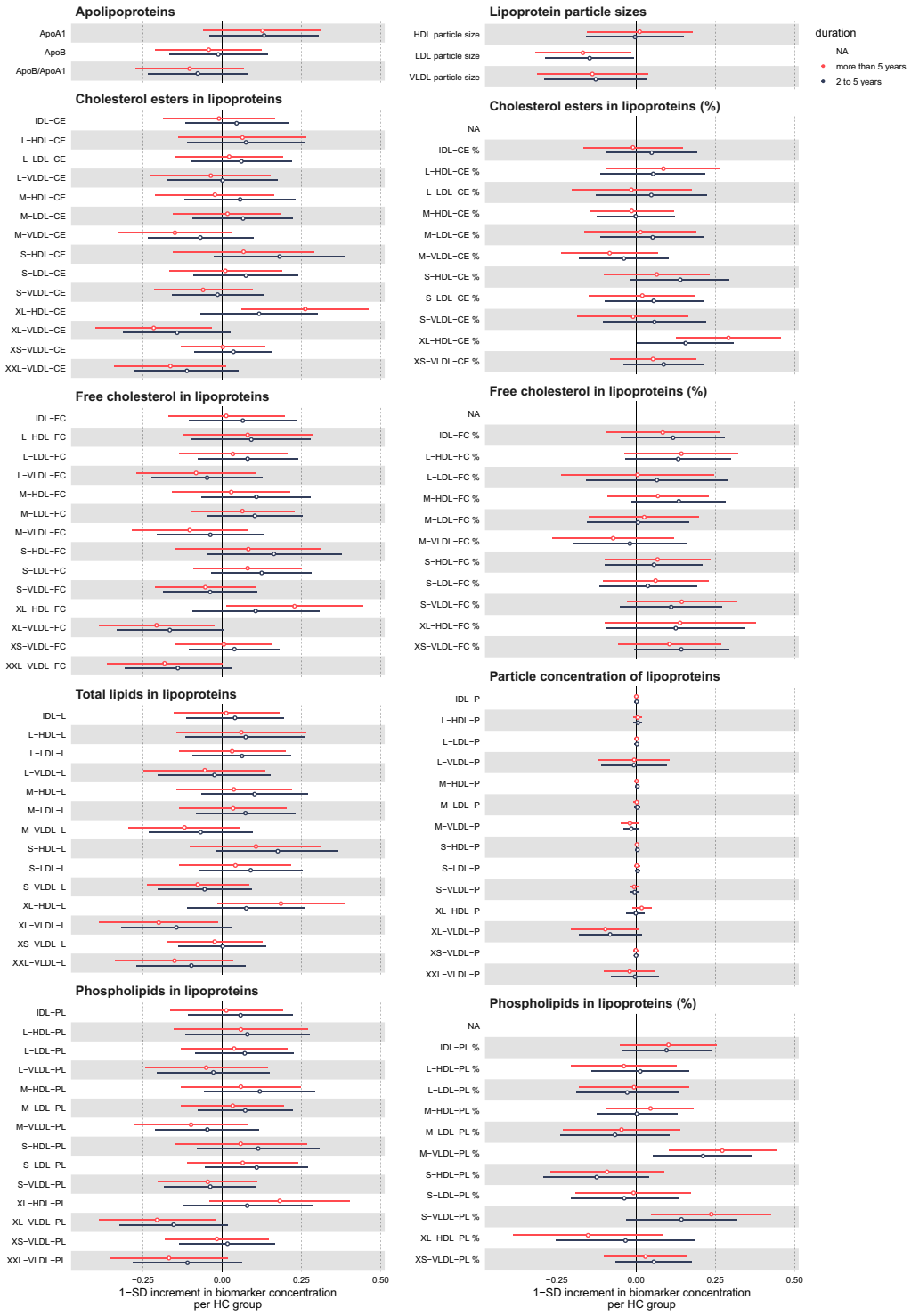

Analyses conducted in the group of current hormonal IUD users only, in the pooled FINRISK 1997, 2002, 2007, and 2012 and FinHealth 2017 surveys. Analyses are adjusted for age, BMI, and study cohort. Results are in SD units of differences in metabolite concentrations; *bars* indicate 95% CI; reference category is short-term (up to 1 year) use of a hormonal IUD. *Closed circles* indicate significant associations at *P* value adjusted for false discovery rate.

BMI, body mass index; *CI*, confidence interval; *IUD*, intrauterine device; *SD*, standard deviation.

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known cross-sectional and prospective markers of insulin resistance, hyperglycemia, and diabetes mellitus.[36,37]

Finally, an important finding of this study were the reduced levels of glycoprotein acetyls, an inflammation marker, in current but not previous users of a hormonal IUD. Increased levels of glycoprotein acetyls have emerged as a predictor of diabetes mellitus, cardiovascular diseases, and all-cause mortality.[38] This result is in line with the previously described protective metabolic profile in hormonal IUD users, and in contrast to the often reported associations of oral contraceptive use with increased proinflammatory status.[16,39]

However, it must be noted that although most of the metabolic changes detected in relation to the use of hormonal IUDs were suggestive of a beneficial metabolic profile, some lipid changes seemed instead to be in the direction of unknown or detrimental effects. In this respect, our study confirmed the previous observations of reduced levels of HDL cholesterol associated with the use of LNG-containing preparations. For example, the use of COCs containing LNG was associated with decreased levels of HDL cholesterol and increased levels of LDL cholesterol and plasma triglycerides.[5] Using metabolomics, we were able to obtain a detailed profile of HDL subfractions, in addition to total levels of HDL cholesterol. Specifically, the HDL particle size was lower, and HDL2 slightly more reduced than smaller and denser HDL3 in users of hormonal IUDs. Low levels of HDL2 are related to dyslipidemic conditions, whereas high levels of HDL3 are related to an increased risk of coronary heart disease.[40] Conversely, a high HDL particle size, along with a reduced level of small HDL and an increased level of large HDL, have been found in diabetic compared with nondiabetic patients.[41]

Research implications

Our results suggest that the use of hormonal IUDs, even for long periods, is not related to long-term metabolic effects. Future research is warranted to assess, in longitudinal settings, whether these findings translate to a reduced risk of cardiometabolic and other-cause morbidity and mortality. Specifically, given the increasing use of hormonal IUDs at young age (and thus, longer periods of exposure), future studies focused on younger age groups are warranted. Because our results essentially pertain only to older reproductive-aged users of 52-mg LNG IUDs, further clinical studies are warranted to examine whether they also apply to younger low-dose hormonal IUD users. Moreover, given that LNG concentration is weight-dependent, and thus its levels are much lower in obese than in nonobese users,[42,43] further analyses should be conducted in more heterogeneous populations with larger proportions of overweight and obese participants.

We could hypothesize that, as a 19-nortestosterone derivative, LNG has residual androgenic activity, which is likely to explain some of the changes associated with the use of hormonal IUDs, such as the effects on lipids. However, further research is required to better understand the mechanisms by which low serum levels of LNG may affect metabolic profiles.

Strengths and limitations

This study has some limitations. The first is related to the homogeneity of our population, which limits the generalizability of the findings. In particular, because most users of hormonal IUDs in our population were aged >30 years, most of our findings only apply to older reproductive-aged individuals, as confirmed by age-stratified analyses. Similarly, although we took BMI into account in our analyses, and approximately 20% of the population were obese individuals, further studies on more heterogeneous populations are required to extend the generalizability of the results. Information on the exact doses of LNG in the hormonal IUDs was not available; however, low-dose hormonal IUDs (13.5 mg and 19.5 mg) have been available in Finland only since 2013; thus, it is plausible that only a small proportion of the 211 hormonal IUD users from the FinHealth 2017 study were using a low-dose hormonal IUD. As such, our results cannot be generalized to one specific hormonal IUD. Another limitation is the lack of information on conditions possibly affecting the type and use of contraception and the metabolic status, such as endometriosis and PCOS. However, we were able to control our results for covariates covering a large set of diseases and confounding conditions. The cross-sectional design of the study further limits the interpretation in terms of causality. Because data were not longitudinal, conclusions on the reversibility of metabolic changes related to hormonal IUD use can only be inferred by retrospective self-reported information on previous use of hormonal IUDs in current nonusers. In addition, given the minor effects of use, the statistical power to detect differences in subgroup analyses, including age-stratified analyses, may be limited. Because of the likely high correlations between several metabolites, interpretation of the implications and importance of single metabolites may have been biased. Thus, the possible clinical implications of our findings are an indirect deduction rather than a direct measure of the real effect. Further studies are needed to confirm our results and their implications. Information on current and previous contraception use and on most of the covariates was derived from self-administered questionnaires; however, self-reports of contraception use have been shown reliable in specifically focused studies.[44,45] In addition, reliability of the data was confirmed through consistency throughout multiple related questions.

The strengths of this study include the large number of participants with available metabolomics data, extensive information on lifestyle and health characteristics, and the large number of available metabolites. By covering a 20-year time period, we were also able to take the trend of growing use of hormonal IUDs in the population into account.

Conclusions

The use of hormonal IUDs was associated with many moderate metabolic

perturbations in an older reproductive-aged population. The metabolic profile of hormonal IUD users indicated reduced arterial cardiometabolic risk. The metabolic effects of hormonal IUD use seemed to be mostly independent of the duration of use, and to not persist after discontinuation of hormonal IUD use. ■

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Author and article information

From the Department of Public Health, Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland (Drs Toffol, But, and Haukka); Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland (Dr Heikinheimo); Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland (Drs Jousilahti and Partonen); Department of Knowledge Brokers, Finnish Institute for Health and Welfare, Helsinki, Finland (Ms Joensuu); Institute of Criminology and Legal Policy, University of Helsinki, Helsinki, Finland (Dr Latvala); and Department of Government Services, Finnish Institute for Health and Welfare, Helsinki, Finland (Dr Erlund).

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O.H. serves occasionally on advisory boards for Bayer AG and Gedeon Richter, and has designed and lectured at educational events of these companies. The other authors report no conflict of interest.

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Data availability: The individual level data used in this manuscript is available through THL Biobank at https://thl.fi/en/web/thl-biobank/for-researchers.

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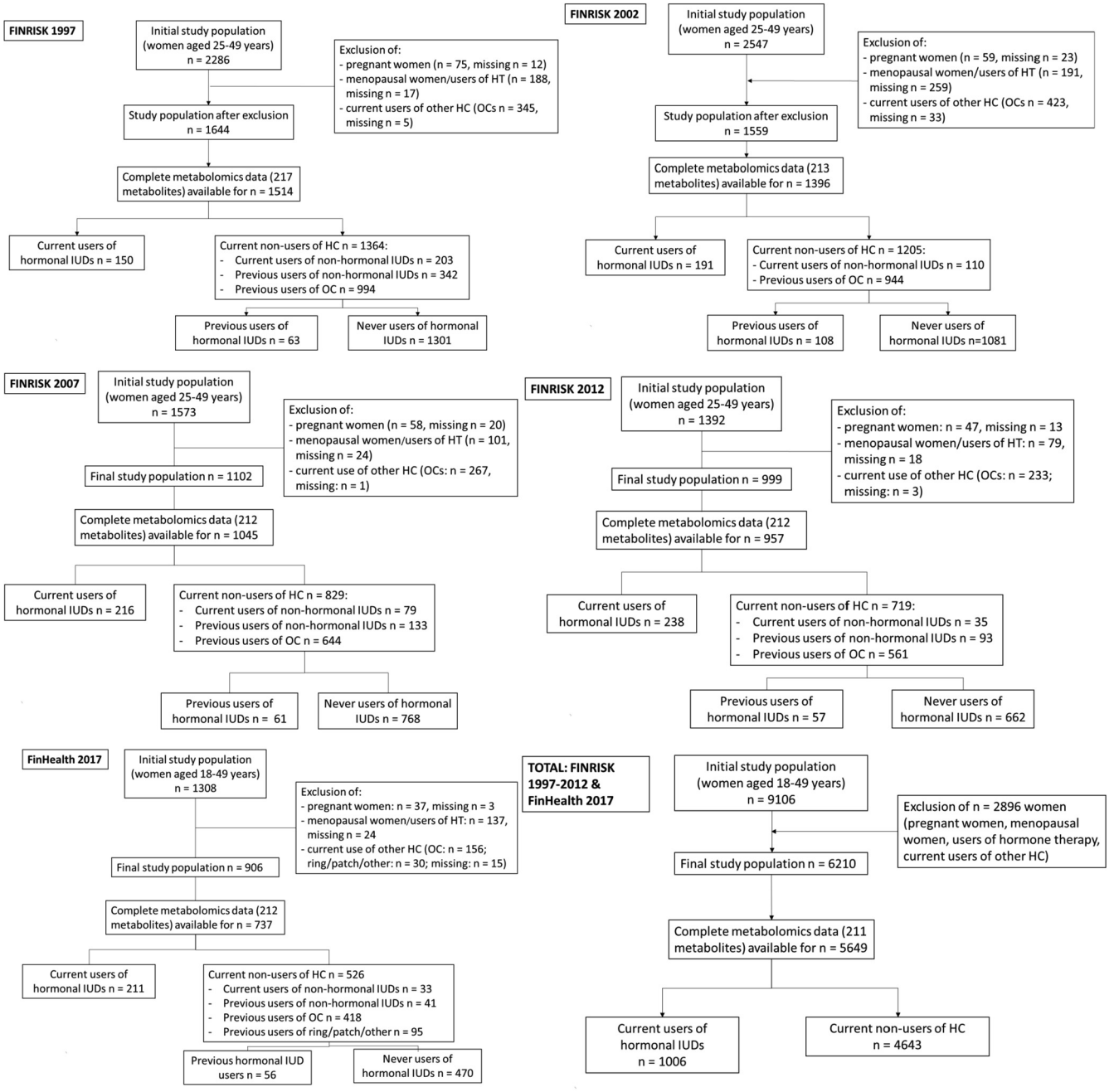
Corresponding author: Elena Toffol, MD, PhD. elena.toffol@helsinki.fi

Appendix

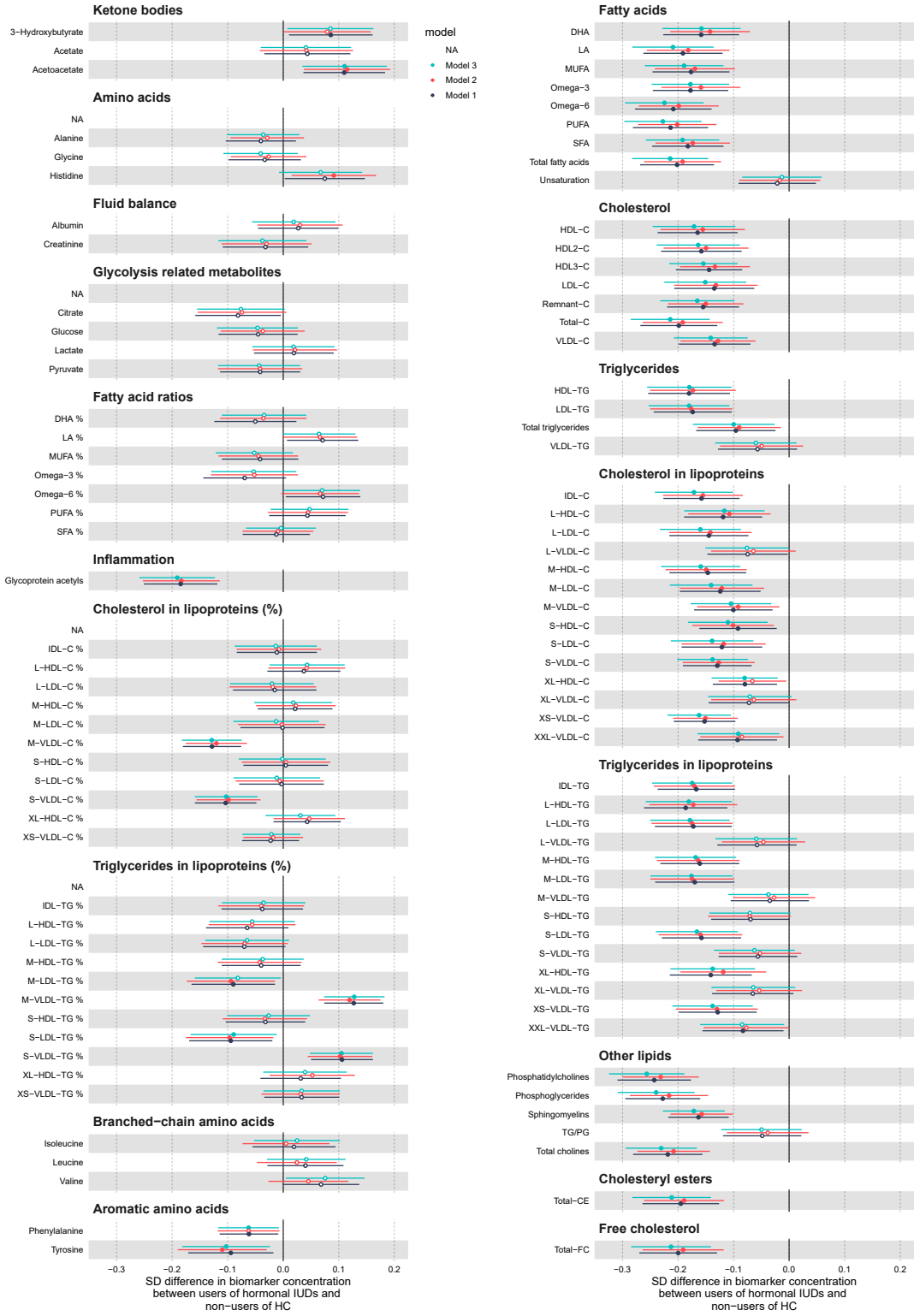
SUPPLEMENTAL FIGURE 1
Selection of study population



HC, hormonal contraception; *HT*, hormone therapy; *IUD*, intrauterine device; *OC*, oral contraceptive.

Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 2
Associations between hormonal IUD and metabolic measures in FINRISK data



Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

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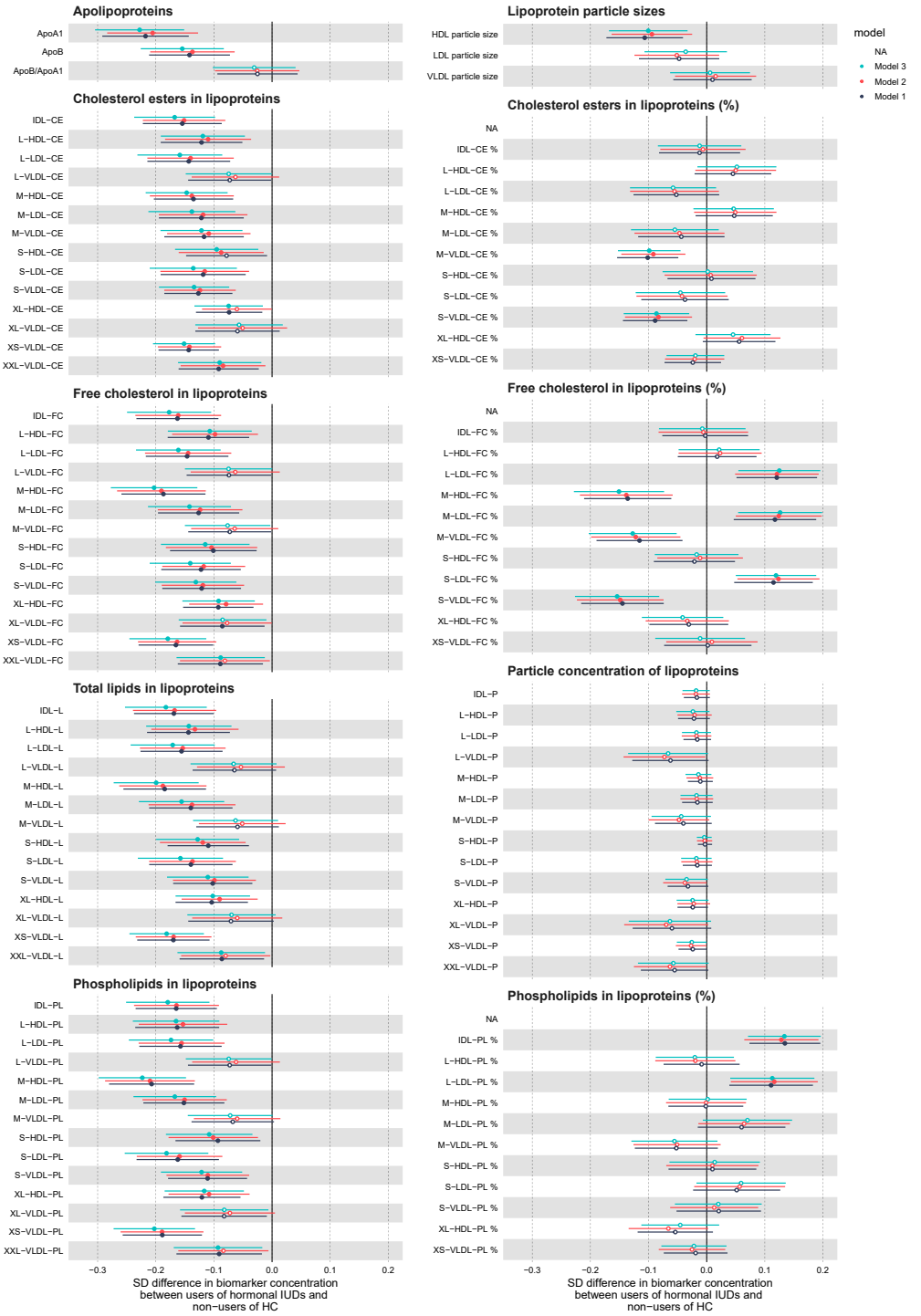
SUPPLEMENTAL FIGURE 2
Continued

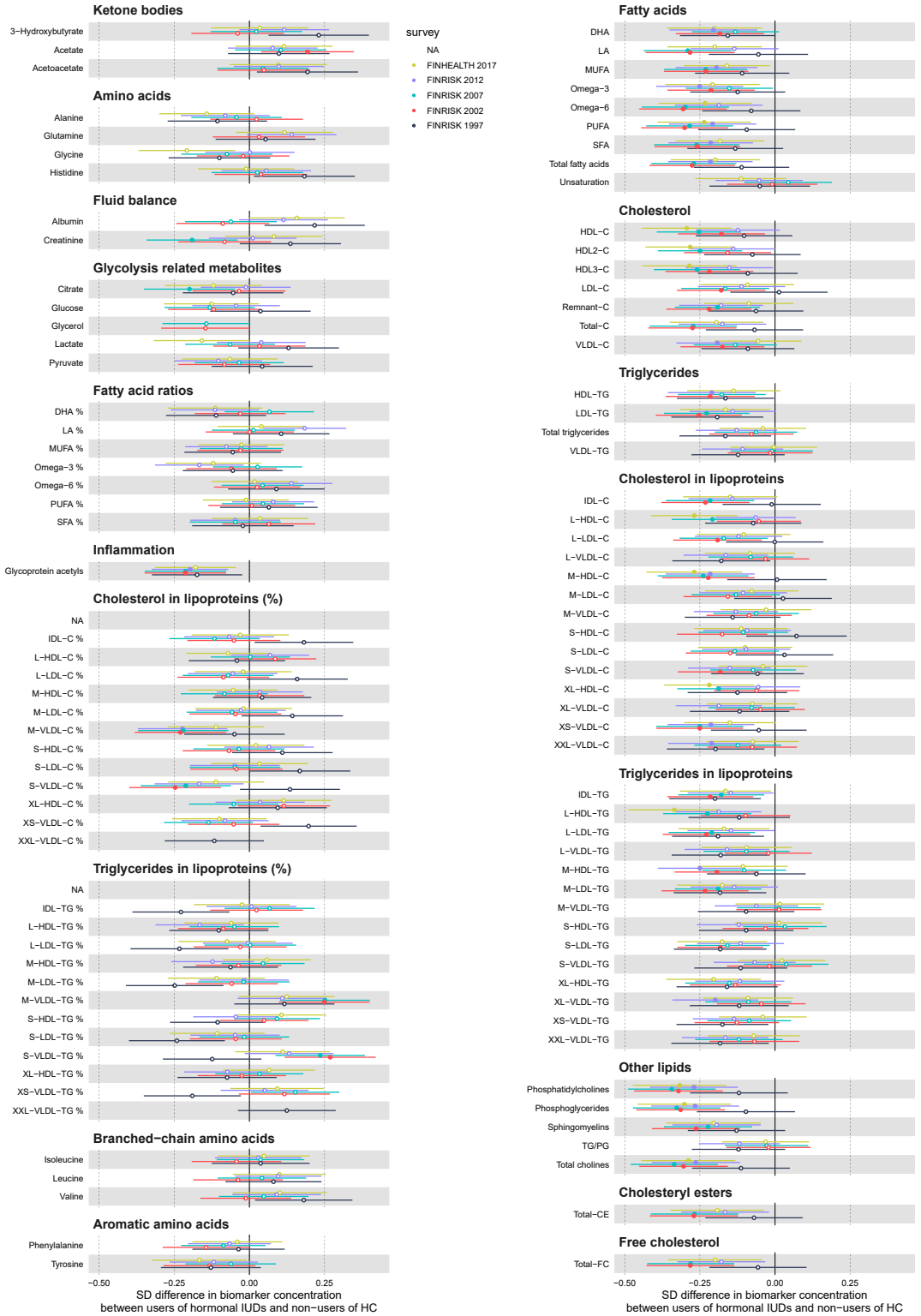


Model 1 is adjusted for age, BMI, and study cohort; Model 2 is Model 1 further adjusted for history of disease and medication; Model 3 is Model 1 further adjusted for alcohol use, smoking, and exercise. Results are in SD units of difference in metabolite concentrations between users of hormonal IUDs and nonusers of HCs; *bars* indicate 95% CI; reference category are nonusers of HCs. *Closed circles* indicate significant associations at *P* value adjusted for false discovery rate.

BMI, body mass index; *CI*, confidence interval; *HC*, hormonal contraceptive; *IUD*, intrauterine device; *SD*, standard deviation.

Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

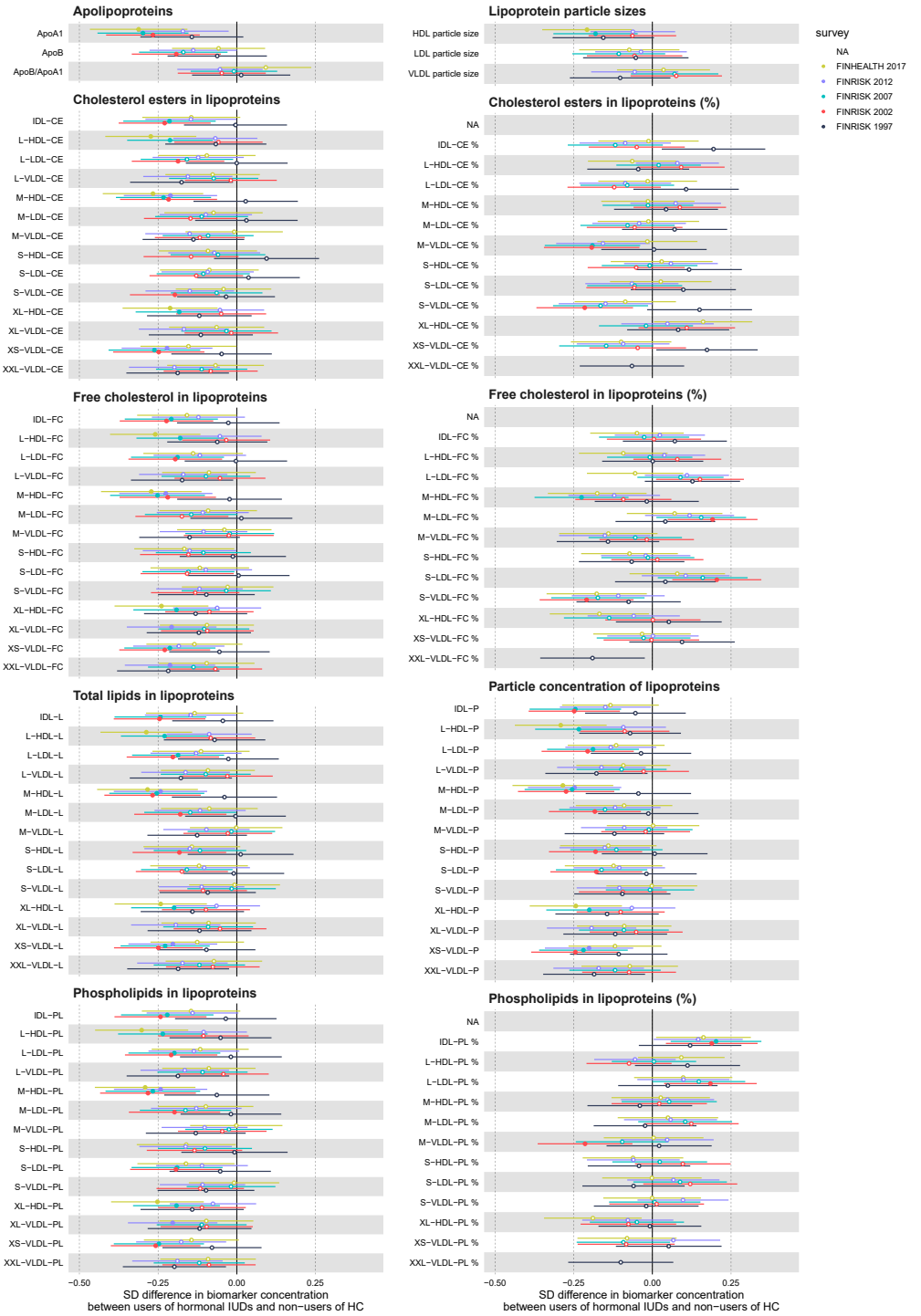
SUPPLEMENTAL FIGURE 3
Associations between hormonal IUD and metabolic measures, Model 1



Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

(continued)

SUPPLEMENTAL FIGURE 3
Continued

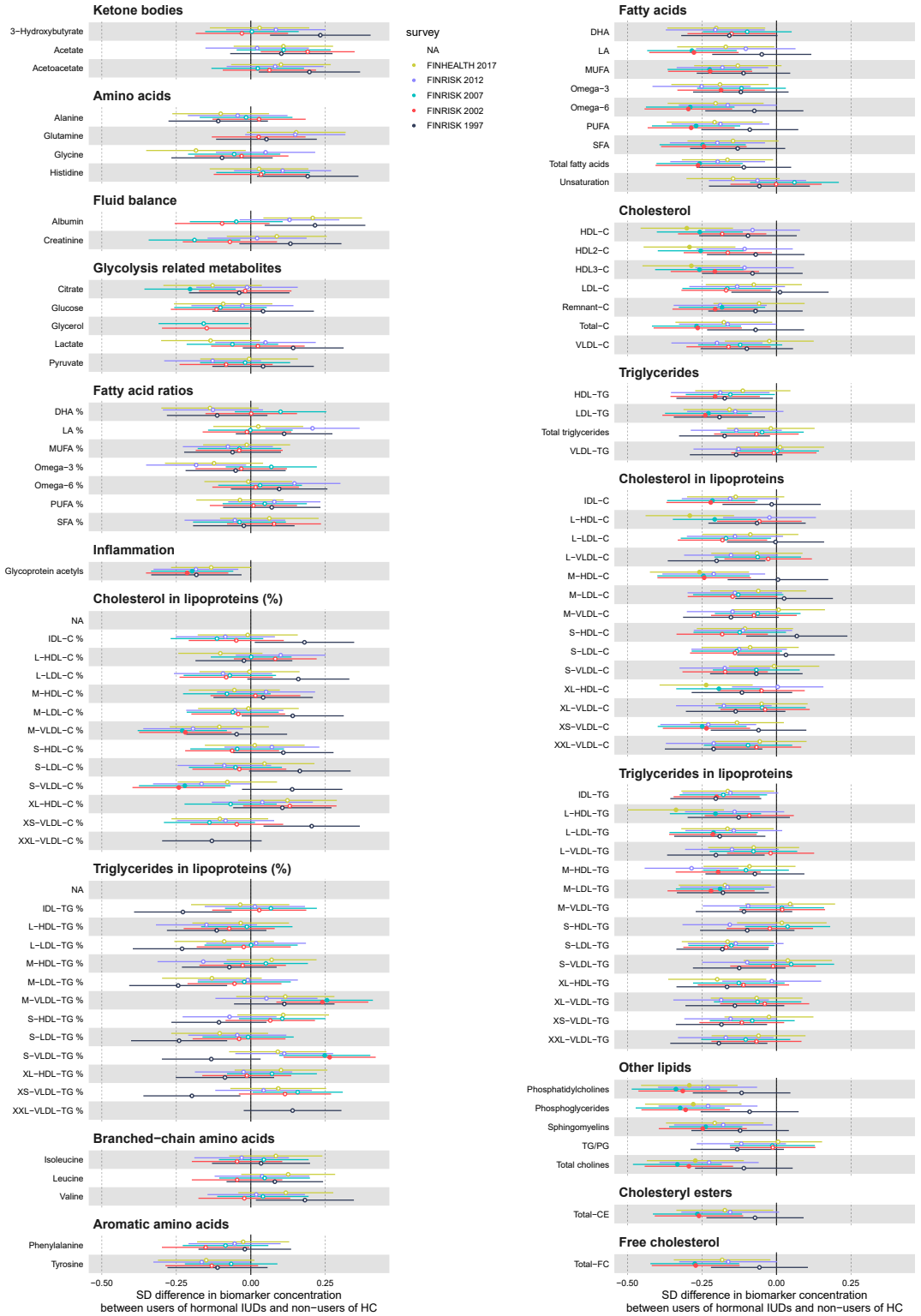


Analyses conducted separately in each FINRISK 1997, 2002, 2007, and 2012 and FinHealth 2017 surveys. Model 1 is adjusted for age, BMI, and season of sampling. The number of examined metabolic measures is n = 217 in FINRISK 1997, n = 213 in FINRISK 2002, n = 212 in FINRISK 2007, 2012, and in FinHealth 2017. Results are in SD units of difference in metabolite concentrations between users of hormonal IUDs and nonusers of HCs; bars indicate 95% CI; reference category are nonusers of HCs. Closed circles indicate significant associations at P value adjusted for false discovery rate.

HC, hormonal contraception; *HT*, hormone therapy; *IUD*, intrauterine device; *OC*, oral contraceptive.

Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 4
Associations between hormonal IUD and metabolic measures, Model 2



Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

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SUPPLEMENTAL FIGURE 4
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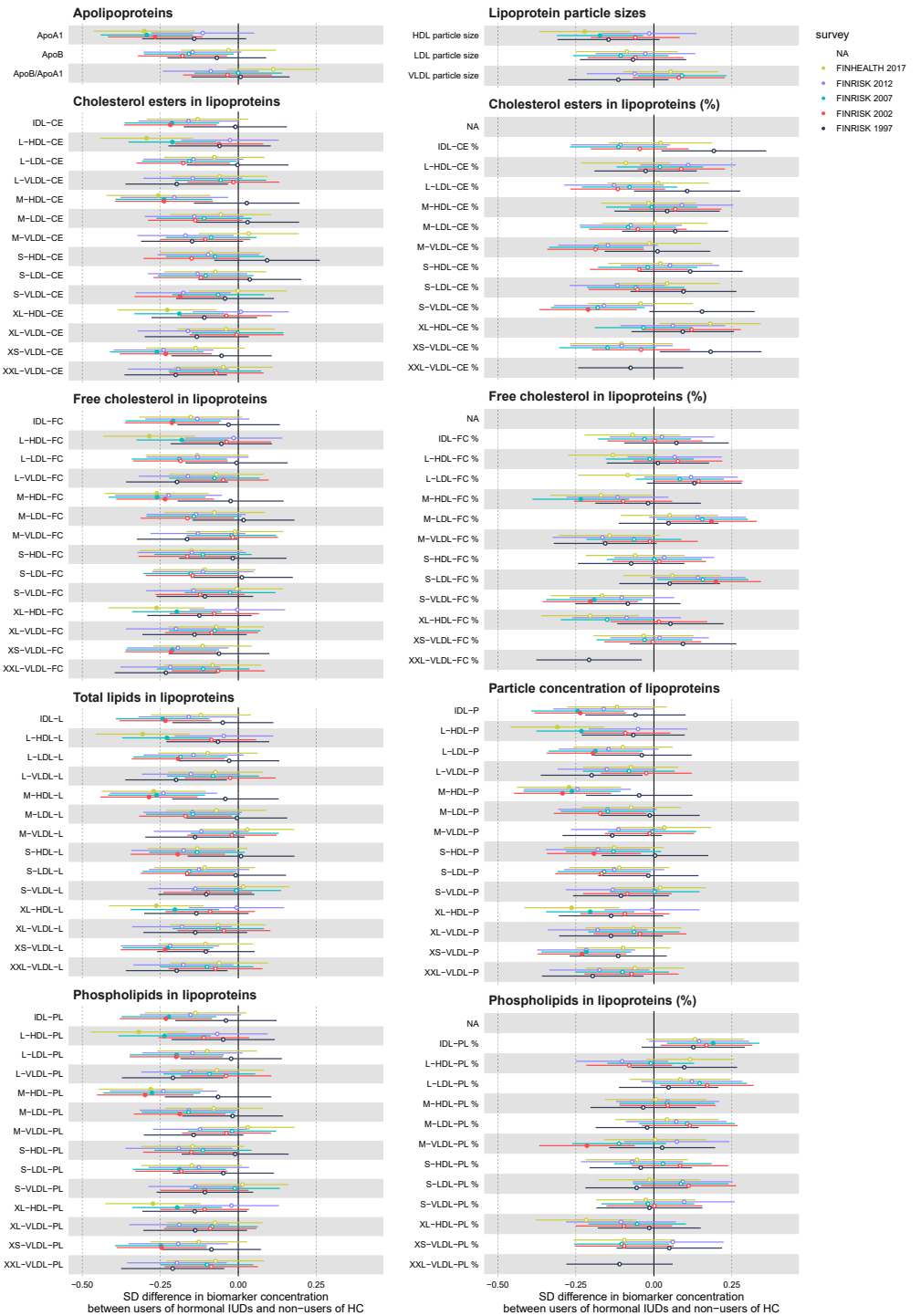
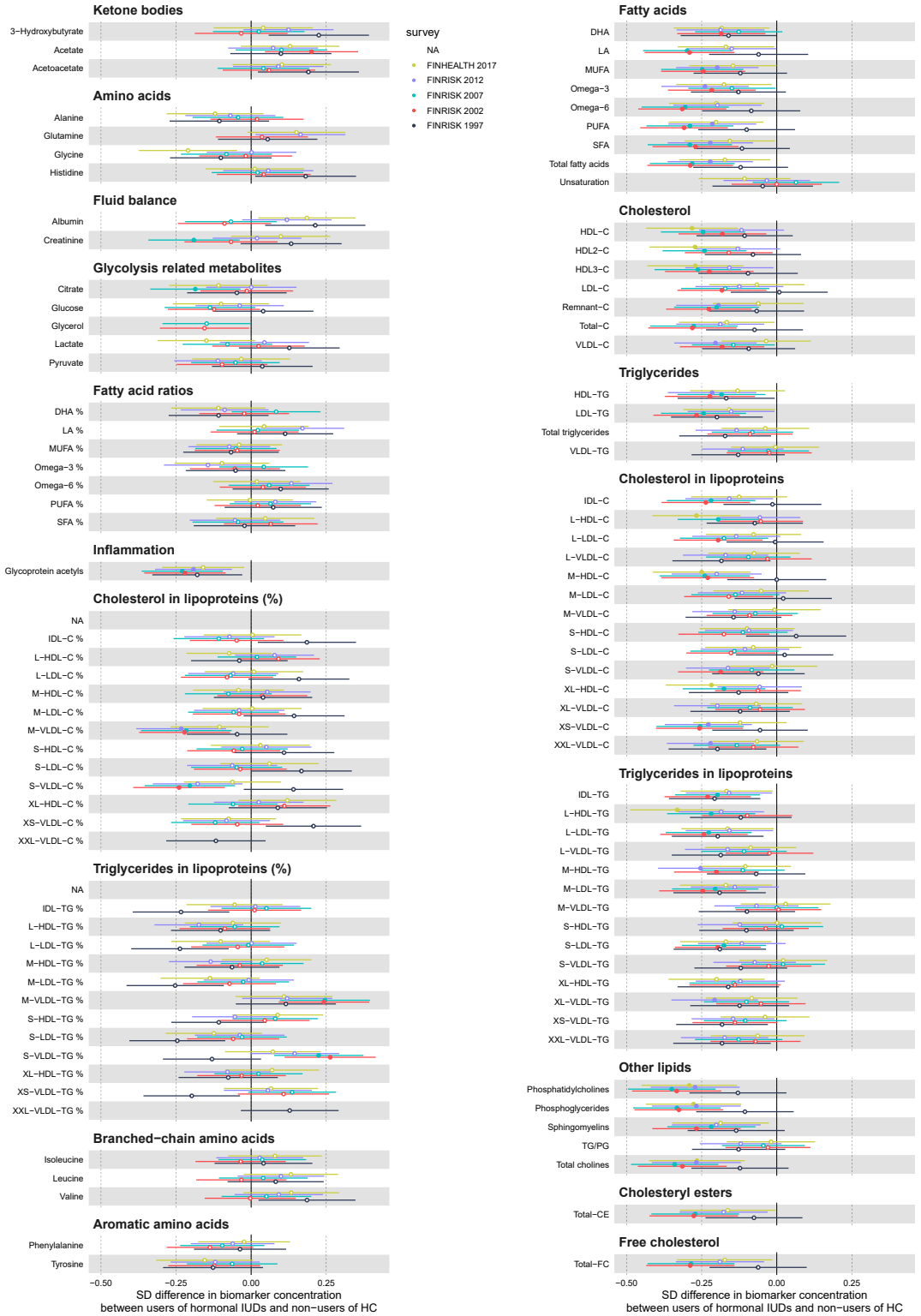


Analyses conducted separately in each FINRISK 1997, 2002, 2007, and 2012 and FinHealth 2017 surveys. Model 2 is adjusted for age, BMI, season of sampling, history of disease and medication. The number of examined metabolic measures is n = 217 in FINRISK 1997, n = 213 in FINRISK 2002, n = 212 in FINRISK 2007, 2012, and in FinHealth 2017. Results are in SD units of difference in metabolite concentrations between users of hormonal IUDs and nonusers of HCs; bars indicate 95% CI; reference category are nonusers of HCs. Closed circles indicate significant associations at P value adjusted for false discovery rate.

HC, hormonal contraception; *HT*, hormone therapy; *IUD*, intrauterine device; *OC*, oral contraceptive.

Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

SUPPLEMENTAL FIGURE 5
Associations between hormonal IUD and metabolic measures, Model 3



Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

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SUPPLEMENTAL FIGURE 5
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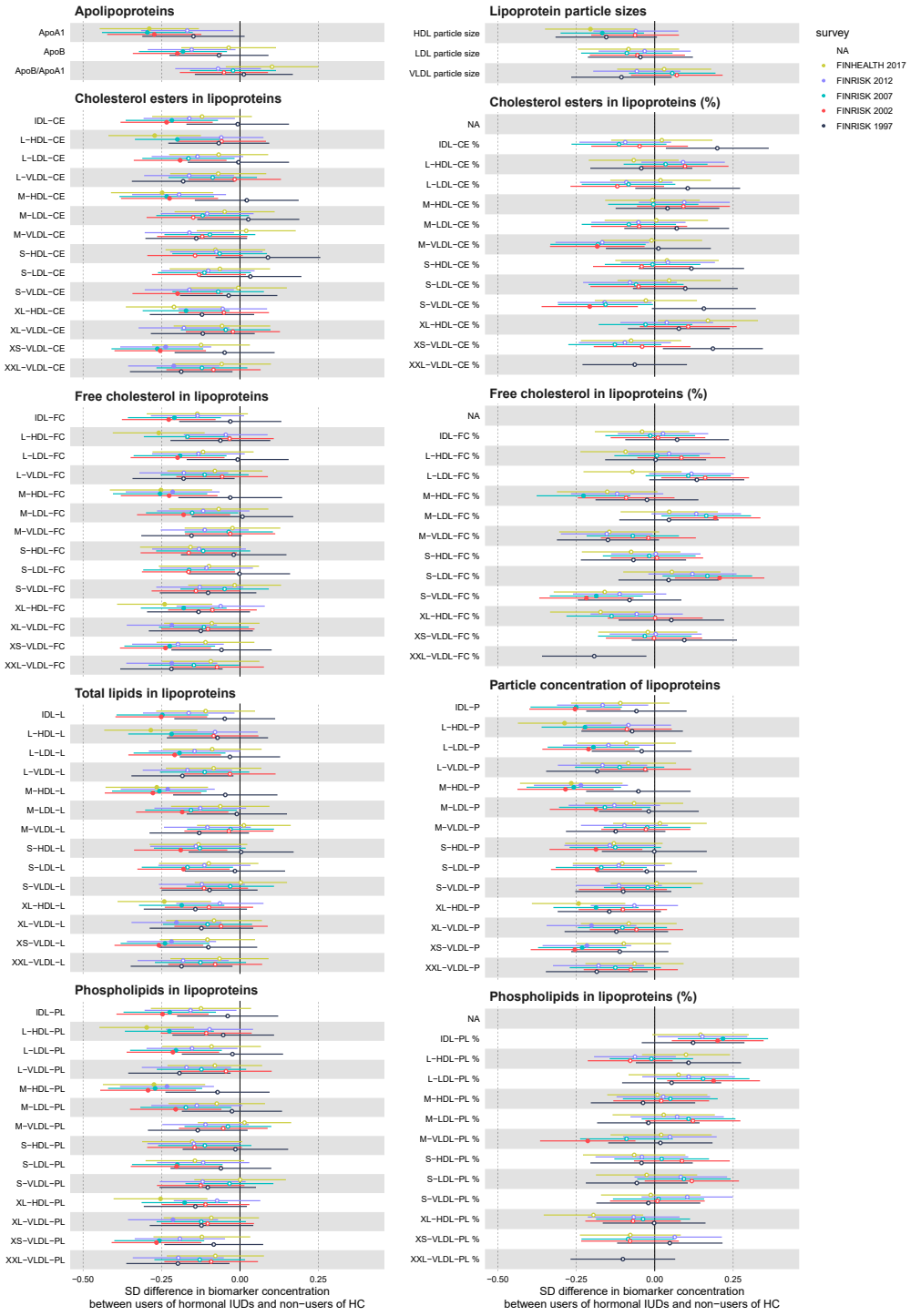

Analyses conducted separately in each FINRISK 1997, 2002, 2007, and 2012 and FinHealth 2017 surveys. Model 3 is adjusted for age, BMI, season of sampling, alcohol use and smoking. The number of examined metabolic measures is n = 217 in FINRISK 1997, n = 213 in FINRISK 2002, n = 212 in FINRISK 2007, 2012, and in FinHealth 2017. Results are in SD units of difference in metabolite concentrations between users of hormonal IUDs and nonusers of HCs; bars indicate 95% CI; reference category are nonusers of HCs. Closed circles indicate significant associations at P value adjusted for false discovery rate.

HC, hormonal contraception; *HT*, hormone therapy; *IUD*, intrauterine device; *OC*, oral contraceptive.

Toffol. Metabolomics of hormonal intrauterine devices. Am J Obstet Gynecol 2022.

SUPPLEMENTAL TABLE 1

Background characteristics of the study population. FINRISK 1997, FINRISK 2002, FINRISK 2007, FINRISK 2012, and FinHealth 2017

	Hormonal IUD users	Hormonal contraception nonusers		Hormonal IUD users	Hormonal contraception nonusers	
	n (%)/mean (SD)		*P* value	n (%)/mean (SD)		*P* value
	FINRISK 1997			FINRISK 2002		
Characteristics	n=150 (9.9%)	n=1364 (90.1%)		n=191 (13.7%)	n=1205 (86.3%)	
Age (range: 25–49 y)	39.4 (5.9)	37.9 (6.8)	.0051	40.4 (5.3)	37.3 (6.9)	<.0001
Age group			.014			<.0001
25–29 y	9 (0.6%)	198 (14.5%)		3 (1.6%)	201 (16.7%)	
30–39 y	63 (42.0%)	547 (40.1%)		74 (38.7%)	505 (41.9%)	
40–49 y	78 (52.0%)	619 (45.4%)		114 (59.7%)	499 (41.4%)	
BMI kg/m^2	25.0 (4.3)	25.0 (4.7)	.95	25.1 (4.4)	25.4 (4.9)	.46
BMI category			.92			.64
Underweight (BMI <18.5)	2 (1.3%)	23 (1.7%)		2 (1.1%)	22 (1.8%)	
Normal (BMI: 18.5–24.9)	88 (58.7%)	791 (58.0%)		112 (58.6%)	660 (54.8%)	
Preobesity (BMI: 25–29.9)	42 (28.0%)	359 (26.3%)		54 (28.3%)	327 (27.1%)	
Obesity class I (BMI: 30–34.9)	13 (8.7%)	117 (8.6%)		15 (7.9%)	123 (10.2%)	
Obesity class II (BMI: 35–39.9)	2 (1.3%)	32 (2.4%)		4 (2.1%)	46 (3.8%)	
Obesity class III (BMI >39.9)	3 (2.0%)	42 (3.1%)		4 (2.1%)	27 (2.2%)	
Season of sampling			.87			.79
Dec–Feb	82 (54.7%)	731 (53.6%)		104 (54.5%)	640 (53.1%)	
March–May	68 (45.3%)	633 (46.4%)		87 (45.5%)	565 (46.9%)	
Alcohol use			.56			.0003
Once/month or more	93 (62.0%)	781 (57.5%)		144 (76.2%)	731 (61.0%)	
Less than once a month	43 (28.7%)	439 (32.3%)		36 (19.1%)	376 (31.4%)	
No/quit	14 (0.9%)	139 (10.2%)		9 (0.5%)	92 (0.8%)	
Smoking			.34			.034
Smoking	42 (28.0%)	334 (24.5%)		52 (27.2%)	342 (28.4%)	
Stopped	39 (26.0%)	345 (25.3%)		46 (24.1%)	189 (15.7%)	
Never smoked	69 (46.0%)	683 (50.2%)		93 (48.7%)	673 (55.9%)	
Physical activity			.88			.86
≥4 times/wk	19 (12.8%)	179 (13.2%)		23 (12.1%)	129 (10.7%)	
1–3 times/wk	98 (66.2%)	873 (64.2%)		125 (65.8%)	823 (68.5%)	
<1 time /wk or disability	31 (21.0%)	308 (22.7%)		42 (22.1%)	249 (20.7%)	
Current use (past week) of any medication[a]	60 (40.5%)	518 (38.4%)	.68	97 (51.6%)	594 (50.5%)	.84
Chronic disease (ever or past year)[b]	68 (46.0%)	573 (42.6%)	.49	91 (48.4%)	580 (49.0%)	.94
	FINRISK 2007			FINRISK 2012		
	n=216 (20.7%)	n=829 (79.3%)		n=238 (24.9%)	n=719 (75.1%)	
Age (range: 25–49 y)	41.2 (5.3)	38.0 (7.1)	<.0001	40.6 (6.4)	37.6 (6.8)	<.0001
Age group			<.0001			<.0001

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(continued)

SUPPLEMENTAL TABLE 1

Background characteristics of the study population. FINRISK 1997, FINRISK 2002, FINRISK 2007, FINRISK 2012, and FinHealth 2017 *(continued)*

Characteristics	Hormonal IUD users n (%)/mean (SD)	Hormonal contraception nonusers	*P* value	Hormonal IUD users n (%)/mean (SD)	Hormonal contraception nonusers	*P* value
	FINRISK 1997			FINRISK 2002		
	n=150 (9.9%)	n=1364 (90.1%)		n=191 (13.7%)	n=1205 (86.3%)	
25–29 y	6 (2.8%)	132 (15.9%)		16 (6.7%)	111 (15.4%)	
30–39 y	66 (30.6%)	318 (38.4%)		76 (31.9%)	304 (42.3%)	
40–49 y	144 (66.7%)	379 (45.7%)		146 (61.4%)	304 (42.3%)	
BMI kg/m^2	25.7 (5.2)	25.8 (5.4)	.84	25.8 (5.0)	25.4 (5.4)	.21
BMI category			.30			.45
Underweight (BMI <18.5)	1 (0.5%)	17 (2.1%)		3 (1.3%)	10 (1.4%)	
Normal (BMI: 18.5–24.9)	124 (57.4%)	426 (51.4%)		122 (51.5%)	396 (55.1%)	
Preobesity (BMI: 25–29.9)	54 (25.0%)	227 (27.4%)		60 (25.3%)	192 (26.7%)	
Obesity class I (BMI: 30–34.9)	20 (9.3%)	89 (10.7%)		35 (14.8%)	70 (9.7%)	
Obesity class II (BMI: 35–39.9)	11 (5.1%)	33 (4.0%)		10 (4.2%)	28 (3.9%)	
Obesity class III (BMI >39.9)	6 (2.8%)	37 (4.5%)		7 (3.0%)	23 (3.2%)	
Season of sampling			.44			.85
Dec–Feb	120 (55.6%)	487 (58.1%)		141 (59.2%)	433 (60.2%)	
March–May	96 (44.4%)	342 (41.3%)		97 (40.8%)	286 (39.8%)	
Alcohol use			<.001			.0007
Once/month or more	164 (75.9%)	502 (60.6%)		147 (61.8%)	428 (59.6%)	
Less than once a month	47 (21.8%)	239 (28.8%)		83 (34.9%)	208 (29.0%)	
No/quit	5 (0.2%)	88 (1.1%)		8 (0.3%)	82 (1.1%)	
Smoking			.42			.51
Smoking	56 (25.0%)	191 (21.9%)		46 (19.4%)	140 (19.6%)	
Stopped	47 (21.0%)	168 (19.3%)		50 (21.1%)	127 (17.8%)	
Never smoked	121 (54.0%)	513 (58.8%)		141 (59.5%)	447 (62.6%)	
Physical activity			.20			.11
≥4 times/wk	39 (18.2%)	198 (23.9%)		60 (29.3%)	143 (24.8%)	
1–3 times/wk	142 (66.4%)	505 (61.0%)		117 (57.1%)	319 (55.4%)	
<1 time /wk or disability	33 (15.4%)	125 (15.1%)		28 (13.7%)	114 (19.8%)	
Sleep duration/24 h	7.6 (1.0)	7.7 (1.2)	.28	7.6 (1.0)	7.7 (1.5)	.50
Current use (past week) of any medication[a]	109 (53.2%)	412 (51.8%)	.78	152 (67.0%)	385 (57.0%)	.0099
Chronic disease (ever or past year)[b]	117 (54.7%)	441 (54.0%)	.92	133 (67.5%)	384 (63.8%)	.39
	FinHealth 2017					
	n=211 (28.6%)	n=526 (71.4%)				
Age (range: 18–49 y)	39.9 (6.3)	36.6 (7.2)	<.0001			
Age group			<.0001			
18–29 y	18 (8.5%)	112 (21.3%)				
30–39 y	59 (28.0%)	198 (37.6%)				

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SUPPLEMENTAL TABLE 1

Background characteristics of the study population. FINRISK 1997, FINRISK 2002, FINRISK 2007, FINRISK 2012, and FinHealth 2017 *(continued)*

Characteristics	Hormonal IUD users n (%)/mean (SD) FINRISK 1997 n=150 (9.9%)	Hormonal contraception nonusers n (%)/mean (SD) FINRISK 1997 n=1364 (90.1%)	*P* value	Hormonal IUD users n (%)/mean (SD) FINRISK 2002 n=191 (13.7%)	Hormonal contraception nonusers n (%)/mean (SD) FINRISK 2002 n=1205 (86.3%)	*P* value
40–49 y	134 (63.5%)	216 (41.1%)				
BMI kg/m^2	26.8 (5.5)	26.0 (5.6)	.11			
BMI category			.67			
Underweight (BMI <18.5)	2 (1.0%)	9 (1.7%)				
Normal (BMI: 18.5–24.9)	98 (46.9%)	262 (49.9%)				
Preobesity (BMI: 25–29.9)	64 (30.6%)	143 (27.2%)				
Obesity class I (BMI: 30–34.9)	24 (11.5%)	61 (11.6%)				
Obesity class II (BMI: 35–39.9)	14 (6.7%)	25 (4.8%)				
Obesity class III (BMI >39.9)	7 (3.4%)	25 (4.8%)				
Season of sampling			.13			
Dec–Feb	57 (27.0%)	174 (33.1%)				
March–May	154 (73.0%)	352 (66.9%)				
Alcohol use			.030			
Once/month or more	119 (56.4%)	262 (50.0%)				
Less than once a month	83 (39.3%)	210 (40.1%)				
No/quit	9 (4.3%)	52 (9.9%)				
Smoking			.71			
Smoking	39 (18.5%)	84 (16.0%)				
Stopped	44 (20.9%)	116 (22.1%)				
Never smoked	128 (60.7%)	325 (61.9%)				
Physical activity			.18			
Do not move much	37 (17.5%)	121 (23.2%)				
Light exercise	91 (43.1%)	223 (42.8%)				
Exercise several hours/week or regularly	83 (39.3%)	177 (34.0%)				
Sleep duration/24 h	7.3 (0.8)	7.3 (1.0)	.40			
Current use (past week) of any medication[a]	118 (57.0%)	270 (52.4%)	.30			
Chronic disease (ever or past year)[b]	122 (58.7%)	302 (58.3%)	1.00			

BMI, body mass index; *IUD*, intrauterine device; *SD*, standard deviation.

[a] Painkillers, anticoagulants, sleeping pills, tranquilizers, antidepressants, hay fever medications, acetylsalicylic acid for preventing myocardial infarction, asthma medications, cholesterol medication, insulin and/or tablets for diabetes mellitus, antibiotics (not available in FINRISK 1997); [b] Asthma ever or in the past year; hypertension ever or in the past year; myocardial infarction, cerebrovascular accident, heightened cholesterol, diabetes mellitus (type 1, type 2, gestational diabetes mellitus), or latent diabetes mellitus ever; cardiac insufficiency, coronary heart disease or angina pectoris, depression, other psychological illness, rheumatoid arthritis, cancer, diabetes mellitus (only in FINRISK 2012), heightened cholesterol (only in FINRISK 2012), back diseases (only in FinHealth 2017), or other joint diseases (only in FinHealth 2017) in the past year.

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SUPPLEMENTAL TABLE 2

Background characteristics of current, previous, and never-users of hormonal intrauterine devices. Pooled FINRISK and FinHealth data

Characteristics	Hormonal IUD current users n=1006	Hormonal IUD previous users n=345	Hormonal IUD never-users n=4282	*P* value
Age (range: 18–49 y)	40.4 (5.9)	41.0 (5.4)	37.3 (7.0)	<.0001
Age group				<.0001
18–29 y	52 (0.5%)	13 (3.8%)	740 (17.3%)	
30–39 y	338 (33.6%)	102 (29.6%)	1767 (41.3%)	
40–49 y	616 (61.2%)	230 (66.7%)	1775 (41.5%)	
BMI kg/m^2	25.7 (5.0)	26.1 (4.9)	25.4 (5.1)	.0016
BMI category				.0078
Underweight (BMI <18.5)	10 (1.0%)	3 (0.9%)	77 (1.8%)	
Normal (BMI: 18.5–24.9)	544 (54.2%)	157 (45.5%)	2368 (55.3%)	
Pre-obesity (BMI: 25–29.9)	274 (27.3%)	123 (35.7%)	1122 (26.2%)	
Obesity class I (BMI: 30–34.9)	107 (10.7%)	37 (10.7%)	422 (9.9%)	
Obesity class II (BMI: 35–39.9)	41 (4.1%)	11 (3.2%)	152 (3.6%)	
Obesity class III (BMI >39.9)	27 (2.7%)	14 (4.1%)	140 (3.3%)	
Season of sampling				.094
Dec–Feb	495 (49.2%)	178 (51.6%)	2269 (53.0%)	
March–May	511 (50.8%)	167 (48.4%)	2013 (47.0%)	
Alcohol use				<.0001
Once/month or more	667 (66.4%)	226 (65.7%)	2472 (57.9%)	
Less than once a month	292 (29.1%)	98 (28.5%)	1365 (32.0%)	
No/quit	45 (4.5%)	20 (5.8%)	432 (10.1%)	
Smoking				.078
Smoking	231 (23.0%)	89 (25.9%)	997 (23.3%)	
Stopped	229 (22.8%)	80 (23.3%)	847 (19.8%)	
Never smoked	545 (54.2%)	175 (50.9%)	2427 (56.8%)	
Physical activity[a]				<.0001
≥4 times/wk	42 (5.6%)	18 (6.4%)	288 (7.9%)	
1–3 times/wk	322 (42.5%)	144 (51.4%)	1887 (51.4%)	
<1 time /wk or disability	393 (51.9%)	118 (42.1%)	1494 (40.7%)	
Current use (past week) of any medication[b]	536 (55.0%)	193 (57.1%)	1975 (47.5%)	<.0001
Chronic disease (ever or past year)[c]	531 (55.6%)	184 (54.6%)	2087 (50.7%)	.015

BMI, body mass index; *IUD*, intrauterine device; *SD*, standard deviation.

[a] Data from FINRISK 1997, 2002, 2007, and 2012 only; [b] Painkillers, anticoagulants, sleeping pills, tranquilizers, antidepressants, hay fever medications, acetylsalicylic acid for preventing myocardial infarction, asthma medications, cholesterol medication, insulin and/or tablets for diabetes mellitus, antibiotics (not available in FINRISK 1997); [c] Asthma ever or in the past year; hypertension ever or in the past year; myocardial infarction, cerebrovascular accident, heightened cholesterol, diabetes mellitus (type 1, type 2, gestational diabetes mellitus), or latent diabetes mellitus ever; cardiac insufficiency, coronary heart disease or angina pectoris, depression, other psychological illness, rheumatoid arthritis, cancer, diabetes mellitus (only in FINRISK 2012), heightened cholesterol (only in FINRISK 2012), back diseases (only in FinHealth 2017), or other joint diseases (only in FinHealth 2017) in the past year.

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