Received: 22 June 2021 | Revised: 24 September 2021 | Accepted: 4 October 2021

DOI: 10.1111/eci.13699

ORIGINAL ARTICLE

WILEY

Changes of lipoprotein(a) levels with endogenous steroid hormones

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Funding information
The SKIPOGH study was supported by grants from the Swiss national science foundation (FN 33CM30-124087/ 140331) and by a grant from the Swiss Heart Foundation (project N. FF17022)

Abstract

Background: Lipoprotein(a) [Lp(a)] is an LDL-like molecule that is likely causal for cardiovascular events and Lp(a) variability has been shown to be mostly of genetic origin. Exogenous hormones (hormone replacement therapy) seem to influence Lp(a) levels, but the impact of endogenous hormone levels on Lp(a) is still unknown. The aim of the study was to assess the effect of endogenous steroid hormone metabolites on Lp(a).

Methods: Lipoprotein(a) levels were measured in 1,021 participants from the Swiss Kidney Project on Genes in Hypertension, a family-based, multicentre, population-based prospective cohort study. Endogenous levels of 28 steroid hormone precursors were measured in 24-h urine collections from 883 individuals. Of the participants with Lp(a) data, 1,011 participants had also genotypes available.

Results: The participants had an average age of 51 years and 53% were female. Median Lp(a) levels were 62 mg/L, and the 90th percentile was 616 mg/L. The prevalence of a Lp(a) elevation ≥700 mg/L was 3.2%. Forty-three per cent of Lp(a) variability was explained respectively by: age (2%, $p < .001$), LDL-C (1%, $p = .001$), and two SNPs (39%, p value$<2{\cdot}10^{-16}$). Of the 28 endogenous steroid hormones assessed, androstenetriol, androsterone, 16α-OH-DHEA and estriol were nominatively associated with serum Lp(a) levels in univariable analyses and explained 0.4%–1% of Lp(a) variability, but none of them reached significance in multivariable models.

Conclusions: In this contemporary population-based study, the prevalence of a Lp(a) elevation ≥700 mg/L was 3.2%. The effect of endogenous steroid hormone levels of Lp(a) variability was small at best, suggesting a negligible impact on the wide range of Lp(a) variability.

KEYWORDS
cardiovascular risk, endogenous hormones, lipoprotein (a)

1 | BACKGROUND

Lipoprotein(a) [Lp(a)] is an LDL-like particle synthesized by the liver that consists of an apolipoprotein B100 molecule covalently linked to the glycoprotein apolipoprotein a, via one disulphide bridge.[1] Lp(a) can enter the arterial intima and Lp(a) levels have been associated with coronary artery disease risk and the risk of stroke. Notably, clinical trial results and Mendelian randomization experiments suggest that elevated levels of Lp(a) are an independent risk factor for cardiovascular disease.[2–4] However, the precise vascular effects of the particle remain unclear for both atherosclerosis and thrombosis.[5] Measurement of Lp(a) should be considered at least once in a person's lifetime with the objective of identifying individuals with very elevated levels who may be at very elevated cardiovascular risk.[6]

Lp(a) concentrations vary widely in the population in a range that spans more than two orders of magnitude. Levels are largely stable over time, a finding to a great extent attributed to differences in the genetic underpinnings of Lp(a) levels. Indeed, a number of single nucleotide polymorphisms (SNPs) in the *LPA* gene region have been identified to be significantly associated with Lp(a) concentrations.[7] Nongenetic factors influencing Lp(a) levels have also been described, for example with severe liver or renal disease.[8,9] Commonly used oral lipid-lowering drugs, such as statins, ezetimibe and fibrates, do not appear to reduce Lp(a) levels significantly. Statins have even been observed to increase Lp(a) levels by around 10%.[10,11] Significant Lp(a) concentration reductions have been observed with nicotinic acid, by up to 35%, through an interference with apo(a) transcription.[12] However, nicotinic acid can lead to significant clinical harm and has not been associated with a cardiovascular benefit in a large randomized trial.[11] On the other hand, both available PCSK-9 inhibitors have been shown to reduce Lp(a) levels by 20%–35%, an effect that appears to reduce cardiovascular risk on top of LDL-C lowering.[13,14]

Among noncardiovascular drugs, hormonal replacement therapy (HRT) is associated with lower Lp(a) levels in some studies.[15] Therefore, it is tempting to speculate that differences in endogenous hormone levels may influence Lp(a) levels and explain, for example, the cardioprotective effects of oestrogens in women.[16]

So far it is unknown if endogenous steroid metabolites are associated with differences in Lp(a) concentrations. The objective of our study was to assess the effect of different endogenous steroid metabolite concentrations on Lp(a) levels in individuals without HRT, hormonal therapy or steroidal derivate treatment (including nebulizers) and estimate if there is any effect on Lp(a) levels. We also evaluated and compared the magnitude of other environmental variables (including genetic variables) actinging on Lp(a) levels in a population-based observational study.

2 | METHODS

2.1 | Population characteristics

We used data and biological materials from participants of the SKIPOGH Study (*Swiss Kidney Project on Genes in Hypertension*—www.skipogh.ch)[17] a Swiss, family-based, multicentre cohort study. In the SKIPOGH study, 400 families from the Swiss general population of European descent were recruited between 2008 and 2011 using a nonstratified sample drawn from lists of inhabitants provided by the population registries of three Swiss cities (Geneva, Lausanne and Bern). The participants were adults aged from 18 to 90 years. A 3-year follow-up was organized between 2012 and 2016, and data from 1,033 participants were available for the current study. Exclusion criteria for the current study were HRT ($N = 9$), other types of hormonal therapies ($N = 10$) and steroid use including nebulizers ($N = 13$). Pregnancy was an exclusion criterion of the SKIPOGH study.

2.2 | Lipoprotein(a) assessment

We used 1,027 plasma samples (389 from Geneva, 391 from Lausanne and 247 from Bern) collected between 2012 and 2016 for the current study. Plasma samples were collected following standard procedures[17] and stored at −80°C until centralized analysis was performed in the Laboratory of Geneva University Hospital. Lp(a) could be measured for 1,021 participants (6 measurement failures). Lp(a) plasma concentrations were assayed by immunonephelometry on a BN ProSpec System (Siemens Healthcare). The quantification limit of the assay was 24.2 mg/L, with insufficient accuracy for concentrations below this threshold. For values below the quantification limit, we imputed the sample value to 17.11 mg/L using a previous described method.$\left(V = \frac{D}{\sqrt{2}} \Leftrightarrow \frac{24.2\ mg/l}{\sqrt{2}}\right)$[18]

2.3 | Steroid metabolite measurement

Twenty-four-hour urine excretion of 28 endogenous steroid hormone precursors and metabolites from 883 individuals was measured centrally by an *in-house* adapted gas chromatography-mass spectrometry (GC-MS) method. Information about the GC-MS method, the method validation for all steroid metabolites, the corresponding calibration curves and quality controls were previously published in detail.[19]

2.4 | Genotyping

All SKIPOGH participants with DNA available were genotyped on Illumina Infinium microarrays (Illumina Inc.) and subsequently imputed using the Michigan Imputation Server.[20] Of the participants with Lp(a) data, 1,011 participants had also genotypes available. We analysed three imputed SNPs, which have previously been associated with Lp(a): rs10455872, rs3798220 and rs3777392.[21,22] Average imputation accuracy was 99.9% for rs3777392, 98.8% for rs3798220 and 83.3% for rs10455872. We used allele dosages for all analyses.

Written informed consent was obtained from all participants prior to inclusion in the study.

Reporting of the study conforms to broad EQUATOR guidelines,[23] in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.5 | Statistical analysis

All statistics were performed using the R statistical software.[24] We calculated means with their standard deviation (±) and medians.

To estimate the association between explanatory variables (co-variates) and Lp(a) levels (outcome variable), linear regression models were fitted using the lm() function and mixed linear regression models with the lmekin().

We used imputed genotype dosages, for a given reference allele, as continuous variable, assuming an additive genetic model.

Variables associated with Lp(a) at a p value <.05 in the univariable analysis were selected to be included in the multivariable analysis. Total cholesterol was replaced with HDL-C to avoid redundancy as LDL-C levels are calculated based on total cholesterol, HDL-C and TG in our dataset. Independent variables were standardized to Z-scores in order to facilitate further visual representation and interpretation of the beta coefficients. The complete set of required co-variables was available in 750 participants. The linear model for the association between Lp(a) level and all selected variables was calculated using the lm() function with Lp(a) levels as nonstandardized dependent variable.

To account for the family relationships, we subsequently utilized a mixed linear model using the lmekin() function included in the coxme package.[25] The random genetic effects expected from the family relationships in SKIPOGH were evaluated with the use of a kinship matrix generated based on the imputation genotypes using PLINK[26] and pc-relate from the GENESIS package.[27,28]

To calculate the statistical power of the multiple regression, we used a noncentral F distribution around noncentral parameter calculated with Cohen's effect size.[29] Considering a sample size of 750, twelve variables and an adjusted R square of 0.52 the present study has 100% power at a two-sided alpha of 0.05.

3 | RESULTS

The mean age of the 1,033 participants randomly recruited from the cities of Geneva, Bern and Lausanne was 51 (±17) years, and both sexes were nearly equally represented (Table 1). BMI, smoking, lipid levels and disease patterns are similar to what has been previously described in the general Swiss population.[30] Lp(a) could be measured for 1,021 participants. We observed a median Lp(a) level

TABLE 1 Baseline characteristics of the study participants with Lp(a) measurement in 1021 participants

Variable	*N*	
Lp(a), mean mg/l ± SD	1,021	151 ± 204
age, mean years ± SD	1,020	50.6 ± 17.3
sex, female–*n* (%)	1,020	538 (53%)
BMI, mean kg/m^2 ± SD	1,016	25.3 ± 4.58
Active smoking	1,010	251 (24.9%)
HTA	1,012	142 (14%)
diabetes type 2	1,012	27 (2.7%)
cardiac disease	1,008	188 (18.7%)
history of TIA/Stroke/MI	1021	36 (3.5%)
Total Chol, mean mmol/l ± SD	1,011	4.98 ± 1.05
LDL-C, mean mmol/l ± SD	1,001	3.07 ± 0.95
HDL-C, mean mmol/l ± SD	1,011	1.52 ± 0.43
TG, mean mmol/l ± SD	1,010	1.04 ± 0.63

Note: The number of individuals analysed and the descriptive statistics are shown for each variable examined.

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HTA, hypertension; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides; TIA, transitory ischaemic attack.

of 62 mg/L (range 17–1,690 mg/L, interquartile range: 363 mg/L). The 90th and 95th percentile were 616 mg/L and 781 mg/L, respectively; three per cent of participants had Lp(a) levels above 700 mg/L (Figure S1A). The distribution of Lp(a) values was similar in the three participant centres, with a right-skewed distribution, in line with previous results (Figure S1B).[31]

We found no significant difference in Lp(a) levels by sex, with a median of 61 mg/L in men and 63 mg/L in women (interquartile ranges 345 mg/L and 378 mg/L).

In univariate analyses, we observed an association of Lp(a) with age (p value = 1.9×10^{-6}, adjusted R^2 = .02), LDL-C level (p value = 1×10^{-3}, adjusted R^2 = .01), triglycerides (p value = .03, adjusted R^2 = .004), hypertension (p value = .03, adjusted R^2 = .004) and two out of the three examined SNPs (rs10455872 A>G: p value = 1.1×10^{-53}, adjusted R^2 = .22 and rs3798220 T>C: p value = 1.1×10^{-40}, adjusted R^2 = .17), as well as with cardiovascular disease (p value = 6.8×10^{-3}, adjusted R^2 = .006) (Table S1). In the 32 participants (3.5%) with very elevated LDL-C levels (≥4.9 mmol/L), the median Lp(a) level was 125 mg/L, almost twice as much as in the entire cohort and 8/32 (25%) had a history of CVD (cardiovascular disease).

We subsequently assessed the association between serum Lp(a) and 28 endogenous steroid metabolite levels measured in 24-h urine in univariate analysis. We found that only four hormones were associated with Lp(a) levels in univariate analysis. Androstenetriol excretion was positively associated with serum Lp(a) levels and explained 1% of Lp(a) variability (p = .002). Androsterone, 16α-OH-DHEA, and estriol explained between 0.4 and 0.6% (p = .01–.03) of Lp(a) variability (see Table S2 for the associations between Lp(a) and all 28 tested endogenous steroid metabolites). These findings did not remain significant after adjustment for multiple testing (p < .00179 by Bonferroni, given 28 tests). The consideration of 28 independent tests is conservative because of the correlation of the steroid hormone metabolite levels among each other.

We tested the effect of three SNPs and found that rs10455872 explained 22% of Lp(a) variability ($p = 2.2 \times 10^{-16}$), while rs3798220 explained 17% of Lp(a) variability ($p < 2.2 \times 10^{-16}$). Both SNPs combined explained 39% of Lp(a) variability. The association between Lp(a) levels and rs3777392 was not statistically significant.

In multivariable regression analyses, the significant variables (age, hypertension, HDL-C, TG, LDL-C, androstenetriol, androsterone, 16α-OH–DHEA, estriol, 5α-TH-corticosterone, rs3798220 and rs10455872) explained 52% of Lp(a) variability. None of the endogenous hormones tested were statistically significant predictors for Lp(a) levels (Table S3). Only age, LDL-C, and rs10455872 and

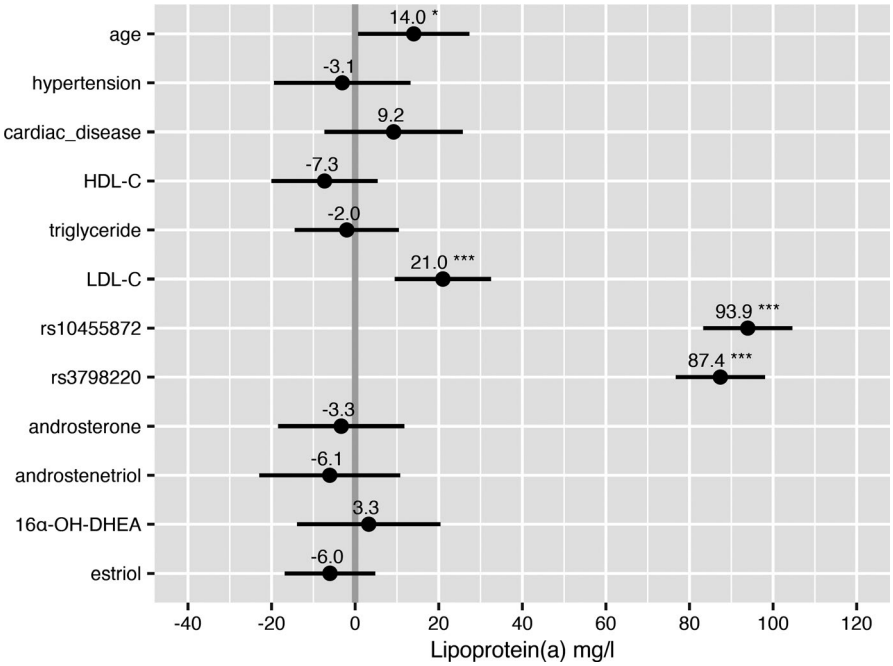

FIGURE 1 Associations of different variables with Lp(a) concentrations in 750 subjects. Associations of different variables with Lp(a) concentrations in 750 subjects. Multivariate regression analysis, with linear mixed-effects kinship models using maximum likelihood estimations were used. The β-coefficients were scaled to Lp(a) levels in mg/L (fixed effects). A total of 750 participants had complete record for all characteristics, 52% of Lp(a) variability is explained by all those variables together, along with the family relatedness. Only age, LDL-C, rs10455872 and rs3798220 are statistically significant with a variability of Lp(a) in mg/L, respectively, of 14 mg/L, 21 mg/L, 93.9 mg/L and 87.4 mg/L. Family relatedness explained up to 138 mg/L Lp(a) variability. Model residual error is 51.5 mg/L. p values: *** <.001 ** <.01 * < .05

rs3798220 remained statistically significant and explained together 43% of Lp(a) variability in the multivariate analysis.

After adjustment for genetic relatedness, in a multivariate analysis using a mixed model, only age, LDL-C, rs10455872 and rs3798220 were statistically significant ($p < .05$) for Lp(a) variability, respectively, of 14 mg/L, 21 mg/L, 93.9 mg/L and 87.4 mg/L (Figure 1).

4 | DISCUSSION

Lipoprotein(a) is considered an independent cardiovascular risk factor and a potentially important therapeutic target.[32] Lp(a) levels were previously considered as non-modifiable, but recent studies have shown that Lp(a) levels can be decreased by 20%–30% with PCSK-9 inhibitors.[14] Additionally, PCSK-9 was also found to decrease cardiovascular morbidity and mortality.[33]

Also, inclisiran and pelacarsen seem decrease Lp(a) levels, but data on mortality are not yet available, and the final proof of establishing Lp(a) as a causal cardiovascular risk factor will be the randomized intervention trial HORIZON[34] that has started in 2020 and will end in 2024.

In this study, we have found a prevalence of Lp(a) elevation ≥700 mg/L of 3.2% in Switzerland. We investigated the association of different environmental variables with Lp(a) levels in a population-based sample from Switzerland. Multivariable analysis explained 52% of Lp(a) variability; age explained 2%, LDL-C 1% and two single nucleotide polymorphisms (rs10455872 and rs3798220) 39%. Lp(a) levels were on average almost two times more elevated in secondary prevention and in individuals with very elevated LDL-C levels (≥4.9 mmol/L), compared to the means of the entire group. Four endogenous steroid hormones assessed (androstenetriol, androsterone, 16α-OH-DHEA and estriol), the presence of cardiac disease, hypertension, HDL-C and triglycerides levels were nominatively associated with serum Lp(a) levels and explained each close to 1% of Lp(a) variability, but they were not associated with Lp(a) levels in multivariable models ($p > .05$).

It has been previously described that sex hormone binding globulin concentrations appear to be independently correlated with Lp(a) concentrations in men.[35] Sex hormones levels are correlated with insulin and glucose levels, and they can increase the cardiovascular risk also in non-obese men.[36] Both of these studies had small sample sizes ($N < 100$).

Hormonal replacement therapy is associated with lower Lp(a) levels, with oral oestradiol leading to larger decreases than transdermal application.[15] Mainly oral oestrogens and tibolone have been specifically studied in postmenopausal women and can reduce Lp(a) concentrations by up to 44%, although evidence indicating a concomitant reduction in CVD risk associated with Lp(a) is lacking.[37] The exact mechanism of the modulation of Lp(a) levels with HRT is still unclear, and our results could be interpreted as an argument against a causal effect of HRT on cardiovascular risk mediated by Lp(a).

Our study is limited because we only assessed associations in participants of European ancestry, and Lp(a) levels vary widely among different ethnic groups[38] with different genetic architectures. The results we obtained are reasonably representative of the overall Swiss population, but with a mean age of the study sample of 50.6 ± 17.3 years, the extremes of the population distribution by age are insufficiently represented.

What are the most favourable Lp(a) levels for cardiovascular risk? Some experts advocate that the levels should be below the 80th percentile of the population distribution (<500 mg/L)[5]; this corresponds to the 92th percentile on our dataset. The threshold is based on data from 6,000 initially healthy subjects from the Copenhagen General Population Study. However, in epidemiological and Mendelian randomization studies performed in primary care populations with no prior cardiovascular disease, cardiovascular disease risk starts at levels as low as 250–300 mg/L.[21] The Copenhagen City Heart Study has not found any threshold effect.[39]

In summary, in this study we did not identify a clear association of endogenous steroid metabolite levels with Lp(a) levels after correcting for co-variates. Given the adequate power of the current study to detect such effects, we conclude that an effect of endogenous steroid metabolite levels on Lp(a) levels is expected to be small, if it exists.

ACKNOWLEDGEMENTS

Open Access Funding provided by Universite de Geneve.

CONFLICT OF INTEREST

FM is national PI of a clinical study by Novartis on Lp(a) lowering, GE is investigator of the same study and has received research grants, consulting, and speaking fees (minor) from Amgen, Boehringer, Daiichi-Sankyo, MSD, Novartis, Recordati, Sanofi, Servier. MP has received consultancy and speaking fees from Novo Nordisk and Astellas.

AUTHOR CONTRIBUTIONS

GE and ET designed the project and obtained funding with FM. GE, ET and KD analysed the data and wrote the manuscript. SE aliquoted the plasma samples tubes. IK and NV performed the measurements of Lp(a) and of 28

endogenous hormones. MB is the SKIPOGH PI and gave critical input for the idea of study design. All authors critically revised the manuscript.

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SUPPORTING INFORMATION

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How to cite this article: Tessitore E, Dobretz K, Dhayat NA, et al. Changes of lipoprotein(a) levels with endogenous steroid hormones. *Eur J Clin Invest*. 2022;52:e13699. https://doi.org/10.1111/eci.13699