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Response to a letter to the editor on "HDL-C and arterial calcification in midlife women: The contribution of estradiol and C-reactive protein"

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We appreciate the insightful comments and questions raised by Dr. Jian Xie and Dr. Lang Li. Below, we address the questions raised by these authors. We agree that a more thorough explanation of our cohort and our methodology makes the research more robust.

We begin by addressing the concerns about calculation of LDL cholesterol. Our cohort had 7 women whose triglyceride level was over 400 mg/dL, whose LDL-C measures ranged from 81 to 197 mg/dL. When we excluded those with high triglycerides from our model, our results were very similar to what we saw previously. The interaction between estradiol and HDL-C was significant with respect to AC with an odds ratio point estimate of 0.96 (95% CI: 0.94, 0.99, p=0.01) and non-significant with respect to CAC, with an OR estimate of 0.98 (95% CI 0.96, 1.01, p=0.18). We also reran our models using the suggested calculation of LDL-C. Our estimates remain consistent with prior models, with a significant interaction observed with regards to AC with an OR point estimate of 0.96 (95% CI: 0.94, 0.99, p=0.01) but not CAC, with an OR estimate of 0.99 (95% CI: 0.96, 1.01, p=0.25). Based on these results and because our primary focus was HDL-C, we assert that our results are robust to this limitation.

Our final models included waist circumference as a measure of adiposity, rather than body mass index. Both BMI and waist circumference are strong predictors of biological and clinical indicators associated with cardiovascular disease, such as blood pressure and lipid

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levels. The two are also highly correlated in our sample (r=0.897, p=<0.0001), and both were found to be significant predictors of both AC and CAC (p<0.0001). In our preliminary analysis, we ran models with BMI and with waist circumference and the c-statistic in model with BMI was slightly lower compared to the model with waist circumference (0.830 vs. 0.834, respectively). Based on model fit alone, we preferred waist circumference as a covariate. In addition, recent literature suggests that visceral adipose tissue increases around the menopausal transition and is associated with greater internal carotid artery intima-media thickness, which we believe supports the clinical significance of waist circumference as a covariate in these models[1]. However, upon receiving this feedback, we ran our models using BMI in place of waist circumference and found the results to be consistent. For AC, the interaction term remained significant in models with BMI, with an odds ratio of 0.96 (p=0.01). For CAC, the interaction term remained insignificant (OR=0.99, p=0.45) in models using BMI. The consistency of these results provides further evidence of the observed association of estradiol on HDL-C with respect to AC.

We agree that multiple imputation is ideal for missing data that are missing at random (MAR). When a lab value is less than the lower limit of detection and we impute within the range of 0 to the lower limit (7 pg/mL), these lab data are not MAR. Instead, we assume that, conditional on having a value less than the limit, the value is MAR restricted to the range of 0 to 7 with a uniform distribution. Given the restricted range of values, this is a reasonable assumption for these missing values. In addition, we performed a sensitivity analysis, which was included as a supplemental table but not discussed at length in our original article, in which we omitted women with estradiol levels below the lower limit of detection, as performed in other SWAN studies[2–4]. Removing women with estradiol levels <7 pg/mL (n=18) from the analysis, we still observed a significant interaction between estradiol and HDL-C with respect to AC (OR=0.97, p=0.01). The association was non-significant with respect to CAC (OR=0.99, p=0.28). Therefore, we believe that our results are robust to the challenges arising from this limitation.

Finally, we want to address the racial makeup of our cohort. The SWAN Heart ancillary study recruited women from two SWAN sites, Pittsburgh and Chicago, which included only Black and White women. SWAN has three sites which recruited Chinese, Japanese and Hispanic women, respectively, in addition to White women. A prevalent theme in SWAN research is the importance of race and ethnicity with regards to outcomes[5]. Therefore, we acknowledge that the results and implications from our manuscript could be generalized to the demographic groups represented in this sample, namely, White and Black women; different associations may be seen among other racial groups. Furthermore, because SWAN is based in the United States, we cannot generalize our results to people living in other nations who may identify as the racial groups studied in SWAN. We believe that the issue of generalizability of our results is important and deserves further research to understand potential differences in these associations between demographic groups.

We believe that these points support our assertion of the link between estradiol and HDL-C on aortic calcification in this cohort of mid-life women. We appreciate the opportunity to expand our discussion of this work and underline the need for additional research to explore this association.

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References:

1. Samargandy S, Matthews KA, Brooks MM, Barinas-Mitchell E, Magnani JW, Janssen I, Kazlauskait R, El Khoudary SR (2021). Abdominal visceral adipose tissue over the menopause transition and carotid atherosclerosis: the SWAN heart study. Menopause. doi:10.1097/GME.0000000000001755
2. El Khoudary SR, Shields KJ, Janssen I, Hanley C, Budoff MJ, Barinas-Mitchell E, Everson-Rose SA, Powell LH, & Matthews KA (2015). Cardiovascular Fat, Menopause, and Sex Hormones in Women: The SWAN Cardiovascular Fat Ancillary Study. The Journal of clinical endocrinology and metabolism, 100(9), 3304–3312. 10.1210/JC.2015-2110 [PubMed: 26176800]
3. El Khoudary SR, McClure CK, VoPham T, Karvonen-Gutierrez CA, Sternfeld B, Cauley JA, Khalil N, & Sutton-Tyrrell K. (2014). Longitudinal assessment of the menopausal transition, endogenous sex hormones, and perception of physical functioning: the Study of Women's Health Across the Nation. The journals of gerontology. Series A, Biological sciences and medical sciences, 69(8), 1011–1017. 10.1093/gerona/glt285
4. Cauley JA, Ruppert K, Lian Y, Finkelstein JS, Karvonen-Gutierrez CA, Harlow SD, Lo JC, Burnett-Bowie SM, Karlamangla A, & Greendale GA (2019). Serum Sex Hormones and the Risk of Fracture Across the Menopausal Transition: Study of Women's Health Across the Nation. The Journal of clinical endocrinology and metabolism, 104(6), 2412–2418. 10.1210/jc.2018-02047 [PubMed: 30690517]
5. Santoro N, & Sutton-Tyrrell K. (2011). The SWAN song: Study of Women's Health Across the Nation's recurring themes. Obstet Gynecol Clin North Am, 38(3), 417–423. doi:10.1016/j.ogc.2011.05.001 [PubMed: 21961710]