To: Sara Brown

Could you comment on the difference in magnitude of association when comparing the effect of obesity on AD vs. the effect of genetically defined obesity?

The magnitudes of effect from observational data and the estimated causality from MR analysis and very similar: In our meta-analyses (Budu-Aggrey et JID 2020) for overweight and obese individuals the OR of AD was ~1.02 per 1kg/m² increase in BMI whilst the effect of higher BMI on AD risk defined by Mendelian randomisation was also OR ~1.02. This suggests that a substantial proportion (if not all) of the causal effect is in the direction of BMI → AD and furthermore, this may explain a large proportion of the observed association.

Is there difference in association of AD and CVD between chronic (childhood onset) and adulthood onset?

We cannot answer that question with our existing data as the duration of follow up is not sufficient, but this is a critically important question that relates to an underlying theory about different outcomes in different AD phenotypes.

To: for Sara Brown

How important is it to account for epigenetic changes which can potentially act as confounding factors in Mendelian randomisation studies?

It is important not to overlook epigenetic factors, but these are actually quite well captured in the genetic instrument, since genome-wide association studies have defined many intergenic risk loci which are likely to represent epigenetic effects.
Cardiovascular diseases are associated with several other inflammatory or immune mediated skin disorders such as Vitiligo. What could be the factors responsible for CVD and abnormal inflammatory response in skin?

There are several potential mechanisms that could contribute to CVD risks in people with skin diseases. One such mechanism might relate to inflammation. However, there are many alternative explanations including adverse lifestyle exposures (including reduced physical activity) associated with stress and stigma, associated cardiovascular risk factors and comorbidities such as associated mental health morbidity. Studying associations between vitiligo and CVD is interesting but challenging. There is limited existing data to my knowledge and studies are small from hospital settings without adjustment for confounders which introduces concerns about selection bias and confounding.

Is it possible that AD patients are protected from obesity?

Yes, this is possible, not least because of the increased metabolic activity associated with pruritus. We did not investigate this in our MR studies because the observational data showed an association of AD with higher BMI.