We read with interest the letter from Meyre (1) about our recently published systematic review and meta-analysis on the associations of variants of the proprotein convertase subtilisine/ kexin type 1 gene (PCSK1) with obesity (2). In his letter, Meyre outlines in 4 criticisms what he perceives to be weaknesses or errors in our paper. We address these criticisms below.

According to Meyre, our meta-analysis included 2 overlapping cohorts (3, 4). Had this been the case, it clearly would have affected the interpretation of our results. However, contrary to his assertion and as Table 1 shows, no overlapping data were included in our meta-analysis. This is also evident from Tables 2 and 3 in our original article (2). The key argument of the letter is therefore incorrect.

In his second point, Meyre suggested that our analysis was underpowered to detect an association in our meta-analysis with obesity (2). In his letter, Meyre implied that we disregarded the established strong association of the rs6232 variant with childhood obesity versus adulthood obesity, we overlooked 2 key studies. However, we agree with Meyre that it is worth considering whether results that were only marginally associated with BMI in published studies turn out to be so in future analyses that include larger sample sizes. We addressed this issue on page 1062 of our article. Nevertheless, it is important to keep in mind the clearly stated purpose of our study, which was to report the results of a systematic review and meta-analysis of relevant data published before December 2013. Thus, because our meta-analysis was, to our knowledge, fully inclusive of studies published up to this date, speculating about how the inclusion of additional materials that do not exist within this timeframe is of questionable merit.

The third point raised by Meyre was that we misinterpreted the literature on PCSK1 variants and obesity. He specifically focused on a section of the Introduction in which we stated that specific PCSK1 single nucleotide polymorphisms (SNPs) were only marginally associated with BMI in published studies. Meyre implied that we disregarded the established stronger associations of other SNPs that are proximal to PCSK1 with BMI. However, in our Introduction, we referred to the literature on SNPs rs6232 and rs6234–rs6235, as these were the focus of our meta-analysis. Meyre appears to have overlooked the section of the Discussion in which we highlighted that 2 other SNPs proximal to PCSK1 have stronger associations with BMI and waist circumference (13, 14).

Finally, Meyre suggested that when we discussed the association of the rs6232 variant with childhood obesity versus adulthood obesity, we overlooked 2 key studies. However, the first of these studies (15), in which analyses compared

<table>
<thead>
<tr>
<th>Table 1. Comparison of Included Cohorts and Potentially Overlapping Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Author, Year (Reference No.)</strong></td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td><strong>Cohorts Included in Our Meta-Analysis (No Overlap)</strong></td>
</tr>
<tr>
<td>Benzinou, 2008 (4)</td>
</tr>
<tr>
<td>Meyre, 2009 (3)</td>
</tr>
<tr>
<td><strong>Cohorts Incorrectly Asserted to Have Been Included in Our Meta-Analyses (Overlap)</strong></td>
</tr>
<tr>
<td>Benzinou, 2008 (4)</td>
</tr>
<tr>
<td>Meyre, 2009 (3)</td>
</tr>
</tbody>
</table>
adults who were younger than 59 years with those who were 59 years of age or older (and therefore were not focused on childhood obesity), is clearly referred to in the Results section of our paper. The paper by Choquet et al. (16), which was also focused on adults, was not cited within this context. Although each of these studies reported meritorious findings, extrapolating findings on the genetics of adult obesity to the pediatric setting would be unwise in our view because of the differences in physiology between these groups. Thus, the novel finding of our study to which Meyre refers is fully substantiated by the evidence, and our decision not to draw strong parallels to studies in adults is fully defensible in our view.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

REFERENCES

8. Colegrave N, Ruxton GD. Confidence intervals are a more useful complement to nonsignificant tests than are power calculations. Behav Ecol. 2003;14(3):446–447.

Pieter Stijnen1, Krizia Tuand1, Tibor V. Varga2, Paul W. Franks3,4, Bert Aertgeerts5, and John W. M. Creemers3 (e-mail: john.creemers@med.kuleuven.be)

1 Laboratory of Biochemical Neuro-endocrinology, Department of Human Genetics, Katholieke Universiteit Leuven, Leuven, Belgium
2 Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University and Skåne University Hospital Malmö, Malmö, Sweden
3 Department of Public Health and Clinical Medicine, Faculty of Medicine, Umeå University, Umeå, Sweden
4 Department of Nutrition, Harvard School of Public Health, Boston, MA
5 Academic Center for General Practice, Department of Public Health and Primary Care, Katholieke Universiteit Leuven, Leuven, Belgium

DOI: 10.1093/aje/kwv061; Advance Access publication: April 9, 2015

RE: “COFFEE CONSUMPTION AND MORTALITY FROM ALL CAUSES, CARDIOVASCULAR DISEASE, AND CANCER: A DOSE-RESPONSE META-ANALYSIS”

In their recent meta-analysis, Crippa et al. (1) reported that coffee consumption is inversely associated with all-cause and cardiovascular disease mortality. The largest risk reduction (21%, 95% confidence interval: 16, 26) was observed for cardiovascular disease mortality at a level of 3 cups/day (1). This remarkable finding should encourage many people to continue, or even increase, their coffee consumption. For once, it will be fairly easy to comply with advice on adopting a healthier diet. Coffee consumption has been reported to have a hypercholesterolemic effect, leading to adverse cardiovascular outcomes (2). Cafestol and kahweol occur naturally in coffee beans and have been identified as hypercholesterolemic compounds (3). The associations of coffee with serum lipoprotein concentrations are largely dependent on the method of its preparation. For example, cafestol and kahweol are not present in regular coffee made with drip coffee-makers, as they are