We are thus heartened by the agreement on the part of Schmidt et al.[1] that the ultimate question is empirical and not theoretical. The suggestion to shun the RD has been made in the belief that it is usually much more heterogeneous than ratio measures such as the OR in empirical research settings. Although there are more heterogeneous possibilities for the RD than for the OR, it would be difficult to defend the assumption that each of those possibilities has the same probability, within or across the many studies that are actually conducted. As noted in our article,[3] further evidence is therefore required before concluding that the risk difference is in fact a more heterogeneous measure.

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TABLE. Total, Direct, and Indirect Effects of Overweight and Obesity on Death from CHD (Compared with Normal Weight) for Metabolic Mediators Systolic Blood Pressure, Total Cholesterol, and Blood Glucose Controlling for Age, Sex, and Smoking Status, VHM&PP Data

Effects	<65 Years		≥65 Years	
	HR (95% CI)[a]	Proportion[b] (95% CI)[a]	HR (95% CI)[a]	Proportion[b] (95% CI)[a]
	Overweight (n = 33,558; 414 Deaths Due to CHD) vs. Normal Weight (n = 56,114; 234 Deaths Due to CHD)		Overweight (n = 4,078; 555 Deaths Due to CHD) vs. Normal Weight (n = 3,522; 471 Deaths Due to CHD)	
Total effect	1.45 (1.21, 1.76)	100%	1.06 (0.93, 1.21)	-[c]
Natural direct effect	1.24 (1.02, 1.52)	58% (10%, 75%)	1.00 (0.88, 1.14)	-[c]
Natural indirect effect	1.17 (1.14, 1.20)	42% (25%, 90%)[d]	1.06 (1.03, 1.10)	-[c]
	Obesity (n = 12,179; 195 Deaths Due to CHD) vs. Normal Weight (n = 56,114; 234 Deaths Due to CHD)		Obesity (n = 1,852; 258 Deaths Due to CHD) vs. Normal Weight (n = 3,522; 471 Deaths Due to CHD)	
Total effect	1.98 (1.58, 2.49)	100%	1.35 (1.15, 1.58)	100%
Natural direct effect	1.44 (1.09, 1.88)	54% (20%, 72%)	1.27 (1.07, 1.50)	80% (40%, 105%)
Natural indirect effect	1.37 (1.25, 1.50)	46% (28%, 80%)[d]	1.06 (0.99, 1.14)	20% (−5%, 60%)[d]

[a]Bootstrapping with 5,000 samples was used to calculate the uncertainty of the estimates.
[b]On ln(HR) scale.
[c]Percentages as proportion of the total effect are not given. Estimates were numerically instable and therefore meaningless due to division by numbers close to zero.
[d]The proportion of the natural indirect effect on the total effect is also called the PERM.[1]
CHD indicates coronary heart disease; CI, confidence interval; HR, hazard ratio; PERM, percentage of excess risk mediated.

Re: Mediators of the Effect of Body Mass Index on Coronary Heart Disease

To the Editor:

The question of how much of the harmful effect of increased body mass index (BMI) on cardiovascular events is mediated through cardiovascular risk factors is of high interest for clinical understanding, public health, and preventive health counseling. Therefore, we appreciate the studies of Lu et al.[1,2] where this topic has been addressed. Major strengths of the study in *The Lancet*[1] are the large number of cohorts included, of the study in EPIDEMIOLOGY[2] the sophisticated methodology. However, we think that the results deserve further discussion.

Since it is well established that the effects of the major metabolic risk factors, including BMI, on cardiovascular diseases decrease with age,[3] we wonder why this interaction effect was not considered in either study. Analyzing data of the Vorarlberg Health Monitoring & Promotion Programme (VHM&PP)[4] which is also part of the earlier study,[1] the interaction term BMI*age suggested a submultiplicative effect of the continuous variables BMI and age on the outcome death from coronary heart disease (CHD, defined via ICD-10 codes I20 to I25). Consequently, we performed mediation analyses assessing

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the combined contribution of systolic blood pressure, total cholesterol, and blood glucose controlling for confounders age, sex, and smoking status separately for younger (<65 years) and older (≥65 years) individuals. We opted for these two age groups because an age of ≥65 years is a common definition of an elderly person. For our analyses, we used the two-stage regression method proposed by VanderWeele[5,6] allowing decomposition of the total effects of the exposure variable BMI into natural direct effects and natural indirect effects. The same method was applied by Lu et al.[2] in their article in Epidemiology. A technical description and R code of the statistical analysis can be found in the eAppendix (http://links.lww.com/EDE/B7).

Our results can be seen below (Table). Our study cohort comprised 111,303 individuals, of whom 2,127 suffered from death due to CHD during a median follow-up of 14.5 years; we excluded individuals with a BMI < 20 kg/m^2. Referring to the interaction mentioned above, age group specific estimates expressed as hazard ratios of overweight/obese versus normal weight individuals were markedly lower in the older age group (see total effects in the Table). For younger individuals, our analyses confirmed the findings of Lu et al.[1,2] that approximately half of the excess risk can be attributed to the risk factors systolic blood pressure, total cholesterol, and blood glucose. For elderly individuals, the total effect of overweight as compared with normal weight was 1.06 (95% confidence interval: 0.93, 1.21) which was fully mediated by the three risk factors. For obesity, there was a total effect of 1.35 (95% confidence interval: 1.15, 1.58); however, the major part (80%) of the excess risk was not explained via the risk factors.

The results of our analyses clearly demonstrate that the analyzed metabolic risk factors play a distinctly different role in explaining the risk of increased BMI on CHD between the younger and elderly population. In higher ages, elevated risk factor levels are not only restricted to overweight or obese individuals but also increase in normal weight individuals[7] (e.g., in our study mean systolic blood pressure was 122.8 mmHg in normal weight individuals <65 years, in ≥65 years 147.7 mmHg). The smaller difference in risk factor levels between normal weight and overweight/obese elderly individuals is the main reason for the reduced relevance of risk factors acting as mediators. In the elderly, obesity presents with an excess risk for CHD mediated only to a small part by the major metabolic risk factors. More than in younger individuals, it appears that risk constellations other than the established pathways (e.g., chronic inflammation) are in play that merit further investigation.[8]

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***The Authors Respond*:**

We had previously considered that the selected mediators (i.e., blood pressure, blood glucose, and serum cholesterol) may explain a different proportion of the effect of body mass index in the elderly versus younger adults. Therefore, in our prior meta-analysis of 97 cohort studies, we stratified the cohorts by mean age at baseline (<55 vs. ≥55 years) and estimated the proportion of excess risk mediated separately. Our results did not indicate any change in proportion of excess risk mediated for coronary heart disease (CHD); and for stroke cohorts with older individuals had a larger proportion of the effect explained by these mediators.[1]

Following the Fritz et al.[2] suggestion, we have now analyzed our

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