Dear Editor:

We thank Drs Peng and Chen for their interest in our recent study on dietary fat and risk of non-Hodgkin lymphoma (NHL) (1). As we reported, total fat intake was borderline significantly positively associated with NHL overall (pooled HR per SD: 1.13; 95% CI: 0.99, 1.29) during the time period 1980–1994. In contrast, there was little evidence for an association during the time period 1994–2010. The 1.29) during the time period 1980–1994. In contrast, there was little evidence for an association during the time period 1994–2010. The

Reply to P-L Peng and P-F Chen

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We thank Drs Peng and Chen for their interest in our recent study on dietary fat and risk of non-Hodgkin lymphoma (NHL) (1). As we reported, total fat intake was borderline significantly positively associated with NHL overall (pooled HR per SD: 1.13; 95% CI: 0.99, 1.29) during the time period 1980–1994. In contrast, there was little evidence for an association during the time period 1994–2010. The positive association observed during the first half of study follow-up was mainly evident in women and was consistent with an earlier analysis in the same cohort (2). Although the association of total dietary fat and all NHL among men during 1986–1994 did not reach statistical significance, we noted a suggestive positive association between animal fat intake and all NHL (HR per SD: 1.16; 95% CI: 0.99, 1.36) and significant positive associations between total, animal, and saturated fat intake and diffuse large B-cell lymphoma in men. Further, we observed no statistical heterogeneity in these associations by sex. Therefore, we interpret this evidence as fairly consistent associations in men and women during this time period.

We agree with Drs Peng and Chen that there are plausible biologic mechanisms by which dietary fat intake could increase NHL risk and that the results of some previous epidemiologic studies support this hypothesis. In particular, we discussed the possible inflammatory, metabolic, and immunologic effects of dietary fats that could contribute to the pathogenesis of NHL as well as the prior epidemiologic literature, including studies with positive findings, in our report. Indeed, we speculated that historically higher intakes of saturated and animal fats could have contributed to observed secular trends in increasing incidence rates of NHL during the earlier part of our follow-up period. Leptin could represent one of many possible pathways to lymphoma development; however, how leptin might explain observed differences in associations of dietary fat and NHL risk by time period is not clear.

Drs Peng and Chen also suggested that case-control studies could minimize the effects of different follow-up periods and small sample sizes in cohort studies and better reflect pre-illness exposure time. However, case-control studies are limited in establishing temporality between exposure and disease and usually have to rely on distant recall to capture exposure history during periods of time prior to diagnosis. Further, there is a strong potential for recall bias in case-control study designs. In other words, the accuracy of recall of past diet (for any given time period prediagnosis) may differ between cases and controls. Because of the large study population, we identified 1802 incident diagnoses of NHL and thus were not limited in sample size even for analyses of the most common histologic subtypes of NHL. Moreover, repeated dietary assessments in these cohorts afforded us the opportunity to explore the most relevant timing of dietary fat intake with regard to NHL risk. When we modelled recent fat intake (compared with cumulative average intake), which might be more consistent with exposure periods assessed in case-control studies, patterns of associations were generally similar to those we reported for cumulative average intake, with positive associations most evident among women in the earliest time period and no clear associations in the more recent time period. Finally, it is not immediately clear that a case-control study design would answer questions about differences in associations by time period; for example, if there is a true difference in associations by time period (e.g., before compared with after 1994), then the results of a theoretical case-control study would certainly depend on what year the case-control study was conducted.

Drs Peng and Cheng propose new prospective studies with adjustment for confounders, yet did not suggest what those confounders might be. In our analyses, we adjusted for age, race, BMI, height, smoking status, physical activity, multivitamin use, and total caloric intake. These covariates were chosen because of known or suspected associations with NHL risk. We cannot rule out an influence of unknown confounders on our findings but are not aware of confounding variables that would explain the unexpected contrast in dietary fat-NHL associations that we observed by follow-up period.

Finally, we would like to take the opportunity to reiterate that compelling evidence points to etiologic heterogeneity in histologic subtypes of NHL (3, 4), which was not mentioned in the letter, but which could have contributed to inconsistent findings in the prior literature. The International Lymphoma Epidemiology Consortium (InterLymph) has recommended that all new epidemiologic studies of NHL include consideration of possible etiologic heterogeneity across common histologic subtypes (5).

The authors declare no conflicts of interest.

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Comments regarding the article “Maternal protein intake in pregnancy and offspring metabolic health at age 9–16 y: results from a Danish cohort of gestational diabetes mellitus pregnancies and controls.”

Dear Editor:

The article by Maslova et al. (1) provides some interesting data about the relation of maternal protein intake in pregnancy to offspring metabolic health, finding no association of such intake to several metabolic measures in the offspring. I also noted with interest that the women with gestational diabetes mellitus were estimated to have a protein intake of 93 g/d, while the control group consumed 90 g/d.

Regrettfully, no mention was made of the evidence that such intakes are higher than recommended for pregnancy, and that, in protein-supplemented women, they have been associated with higher rates of very early preterm delivery with increased neonatal deaths (2). This finding was supported by another study using the same protein supplement (3), where infants of the protein-supplemented women had a mean birth weight 45 g lower than infants of un-supplemented women, whereas the infant birth weight of women given a balanced protein and calorie supplement was 92 g greater than that of the unsupplemented women. Further, in a study of spontaneous protein intakes of recipients of WIC (the Special Supplemental Program for Women, Infants and Children) (4), mean protein intake ≥85 g/d was associated with a 71-g lower birth weight compared to infants of women with an intermediate intake (50–84.9 g/d).

Readers should be aware that high-protein diets are not ideal for pregnant women, even if they do not affect the offspring’s metabolic health.

The author has no conflicts of interest.

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Reply to SA Lederman

Dear Editor:

We thank Dr Lederman for her interest in our paper and for allowing us to delve deeper into this complex issue. Dr Lederman points out some of the adverse perinatal outcomes of protein supplements and intake in pregnancy, stemming primarily from randomized clinical trials conducted in 1970s and 1980s (1–3). We acknowledge that these are important cautionary notes; however, they need to be framed within their relevant biological and epidemiologic limitations.

First, it is notable that the populations where an association was found with fetal growth restriction, prematurity (3), and birth weight (1) tended to be of lower socioeconomic status and likely undernourished based on the anthropometric and nutritional data presented in the papers. The trial by Adams et al. (2) was conducted in well-nourished women, among whom only 3 women delivered infants with low birth weights, of which 1 was in the high protein group and 2 in the control (vitamin-mineral supplement) group. They concluded that there was no association of protein supplement with birth weight, despite a trend towards higher birth weight with higher protein intake. This is similar to findings in the Danish National Birth Cohort where protein intake from dairy products was associated with higher birth weight (4). It is plausible to posit that maternal size before pregnancy may modify the response to nutritional changes in pregnancy; whether this is related to maternal metabolism, placental development, changes in the endocrine milieu, or other factors is still far from clear. We know from past studies that maternal undernutrition influences placental structure and function as well as hormone concentrations, including those that regulate fetal growth (5, 6). Importantly, data derived mainly from animal studies, supported by human observations, indicate that under conditions of undernutrition, maternal maintenance of body weight is favored over fetal growth, even when nutritional supply is re-established (6). We could therefore interpret the results of these past studies on protein among undernourished populations as a prioritization of maternal over fetal nutrition. This can also be viewed in light of the parent-offspring conflict theory as it applies to early development of health and disease, where maternal investment in individual fetal growth is reduced to benefit the mother’s lifetime reproductive fitness (7, 8). These arguments are not incompatible with Dr Lederman’s points, but rather an extension of the discussion to recognize the contextual factors. Supplemental protein intake that is not balanced against calories may indeed create an adverse intrauterine environment, but since the trial by Rush et al. (3) was conducted in the 1970s in poor communities where neonatal care would have been far from current standards, the outcomes may not be generalizable to contemporary populations living in high-income countries. More work is needed to better understand how contextual factors such as maternal size may modify response to nutritional factors in pregnancy. These studies should