Abstract: Birth weight in offspring and cardiovascular mortality in their parents, aunts and uncles: a family-based cohort study of 1.35 million births

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Introduction: A link between suboptimal fetal growth and higher risk of adult cardiovascular disease (CVD) has been demonstrated within individuals and across generations in several populations. Common genetic factors may be responsible for this association, but it has been difficult to assess the contribution of behavioral/environmental verses genetic factors because within nuclear families these factors are closely linked.

Aim: To investigate if the association observed between offspring birth weight and parental CVD mortality can also be observed with respect to the aunts and uncles of the offspring, and investigate whether these associations are explained by well-known CVD risk factors.

Methods: We linked Norwegian data from multiple cardiovascular surveys, the Medical Birth Registry, the Cause of Death Registry and the Education Registry to create a cohort. Parents’ siblings were identified by a multigenerational database, using unique personal identity numbers. The final dataset comprised of 1,353,956 births (1967-2012) linked to both parents and one maternal and one paternal sibling (i.e. aunts/uncles of the proband births). Associations between offspring birth weight and CVD mortality among parents and aunts/uncles were assessed by hazard ratios (HR) from Cox regressions. The possible influence of CVD risk factors on the association was assessed in a subgroup for which risk factor data were available from the health surveys.

Results: Offspring birth weight was inversely associated with CVD mortality among their parents and their aunts/uncles. HR of CVD mortality for 1-SD increase in offspring birth weight was 0.72 (0.69-0.75) in mothers and 0.89 (0.86-0.92) in fathers. In aunts/uncles, the HR were between 0.90 (0.86-0.95) and 0.93 (0.91-0.95). Adjustment for education attenuated the associations in parents, aunts and uncles. Adjustment for CVD risk factors and education in a subgroup attenuated all the associations.

Conclusion: We show that offspring birth weight was associated with increased risk of CVD in parents and in aunts/uncles, and these associations were influenced by CVD risk factors. The strong association in mothers suggests an intra-uterine effect which may be genetic or environmental. Our study emphasizes the importance of shared environmental factors on birth weight and CVD association along with genetic factors.