"Looking Old for Your Age": Genetics and Mortality

To the Editor:

When assessing health, physicians traditionally compare perceived and chronologic age. Among adults, "looking old for your age" is often interpreted as an indicator of poor health. The sparse data available on the relation between perceived age and survival indicate an inverse association.[1] It is not known whether "looking old for your age" is primarily a result of lifestyle and other environmental factors or whether genetic factors play an important role. Here we use a population-based survey of Danish twins, age 70 years and older, to assess whether perceived age is influenced by genetic factors and whether "looking old for your age" is associated with an increased mortality.

In the 2001 survey of the Longitudinal Study of Aging Danish Twins,[2] 91% of cognitively intact participants agreed to have their picture taken (using a digital camera at 0.6-meter distance, with a neutral background, whenever possible). For a total of 387 same-sex twin pairs, we had a high-quality picture of both twins: 82 sets of monozygotic males, 93 monozygotic females, 94 dizygotic males, and 118 dizygotic females. The twins were not all photographed with neutral facial expressions, but according to Sheretz et al.,[3] this has no effect on age estimation.

We engaged 20 female nurses (age 25 to 46 years) to estimate the twins' ages based on digital photographs. The nurses were not informed beforehand about the age range of the twin pairs. They estimated the ages of all first-born and second-born twins on different days. The mean of the nurses' age estimates for a twin was used as the twin's perceived age. The reliability of the mean age rating was estimated at 0.94 from a one-way analysis of variance. The correlation between real age and perceived age was 0.40 (95% confidence interval [CI] = 0.32–0.48), and the table shows that the nurses' estimates regressed toward a mean of 77.

The intrapair correlation for perceived age within monozygotic twins (r = 0.59; CI = 0.49–0.68) is approximately twice the correlation for dizygotic twins (r = 0.29; CI = 0.16–0.41) (Table 1). These findings indicate an effect of additive genetic factors[4] influencing perceived age. The correlations did not vary by age group or gender. Biometric models[4] confirmed that the twin similarity is best explained by a model including additive genetic factors and nonfamily environment, and that the heritability (ie, the proportion of the variance explained by genetic factors) of perceived age is approximately 60% with no sex or age differences.

By January 2003, nearly 2 years after having been photographed, at least one of the pictured twins in 49 pairs had died. Among these 49 pairs, the longer-surviving twin had been rated as looking younger, on average, than his or her cotwin (mean of 1.15 years; CI = 0.11–2.19). This difference, however, owed entirely to those twin pairs who were perceived to be discrepant in age. Among the 26 pairs for which perceived age differed by 2 or more years, the oldest-looking twin died first in 19 (73%) cases, verifying that perceived age is associated with mortality. Stratifying these analyses for zygosity revealed zygosity differences: among 16 dizygotic twin pairs, the oldest-looking twin died first in 13 (81%) cases, whereas for the 10 monozygotic pairs, the oldest-looking twin died first in 6 (60%) cases. The numbers are small, but this pattern suggests that there are common genetic factors influencing both perceived age and survival, because controlling for genetic factors (the within monozygotic comparison) attenuates the association between perceived age and survival.

In summary, we show that approximately 60% of the variation in perceived age among twins can be explained by genetic factors and that "looking old for your age" is associated with increased mortality. Genetic factors are important for a broad range of traits and conditions from behavioral phenotypes, anthropometrics, and diseases to physical and cognitive functioning.[5] Our design cannot determine how the genetic influence on perceived age is mediated. Nonetheless, our biometric models indicate that the genetic effects are acting additively, which suggests that "looking old" (or "looking young") is a trait likely to run in families.

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TABLE 1. Real and Perceived Age in Danish Twins Age 70+ Years

Age Range (years)	70–74	75–79	80+	All (70+)
No. (MZ, DZ)	200 (86,114)	119 (51,68)	68 (38,30)	387 (175,212)
Real age, mean (SD)	72.3 (1.4)	77.4 (1.5)	83.4 (2.9)	75.8 (4.5)
Perceived age, mean (SD)	75.4 (2.9)	78.0 (2.7)	77.7 (3.3)	76.6 (3.2)
MZ correlation*, r (95% CI)	0.59 (0.43–0.71)	0.55 (0.32–0.71)	0.66 (0.43–0.81)	0.59† (0.49–0.68)
DZ correlation*, r (95% CI)	0.26 (0.08–0.43)	0.33 (0.10–0.53)	0.32 (−0.04–0.61)	0.29† (0.16–0.41)
Heritability*, r (95% CI)	0.57 (0.43–0.68)	0.54 (0.36–0.68)	0.65 (0.43–0.79)	0.58† (0.48–0.65)

*Intrapair correlation for perceived age.
†Age-adjusted residuals used to control for age.
MZ, monozygotic; DZ, dizygotic; SD, standard deviation.

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Body Mass Index and Preeclampsia

To the Editor:

In a study recently published in EPIDEMIOLOGY, O'Brien and colleagues[1] presented results of a metaanalysis examining the relation between prepregnancy body mass index (BMI) and risk of preeclampsia. Quantifying this relation is of major public health importance given the increasing prevalence of obesity, as well as the high risk of maternal and neonatal morbidity and mortality associated with preeclampsia. However, results from this overview should be interpreted with caution because the component studies did not estimate a common causal parameter.

The authors included 13 studies in their metaanalysis. For 4 of these studies,[2–5] only unadjusted odds ratios for the BMI–preeclampsia relation were presented. It is likely that unmeasured confounding by sociodemographic variables and health-related behaviors biased these effect measures.

Multivariate analyses were conducted for the remaining 9 studies.[6–14] Of these, 2[6,7] presented results from a causal model (ie, measured confounders were used to adjust the BMI–preeclampsia odds ratio). Three others[8–10] had BMI as the primary exposure, but adjusted for variables such as chronic hypertension and gestational diabetes, which are likely on the causal pathway from BMI to preeclampsia.[15] The adjusted effect estimates therefore do not represent the total causal effect of BMI, but rather its direct effect, the portion not relayed through these intermediates.[16]

The final 4 studies using multivariate methods[11–14] presented adjusted odds ratios derived from predictive models. The objective of predictive modeling is not to determine the causal effect of an exposure on the outcome, but to best predict the outcome by including all variables associated with it.[17] Unlike causal modeling, confounding is not an issue in predictive modeling because there is no "primary exposure." Including variables that are potentially intermediates on the pathway between a predictor and the outcome is not a problem. Therefore, adjusted odds ratios derived from predictive modeling do not necessarily have causal interpretations and may bias the results of metaanalyses.[18]

Additionally, O'Brien and colleagues[1] included papers that examined either preeclampsia (gestational hypertension and proteinuria) or gestational hypertension alone,[1] yet these outcomes are recognized as separate entities[19] with different risk factors and clinical findings.[20] To assess the causal effect of prepregnancy BMI and hypertensive disorders of pregnancy accurately, subclassification may be preferred.[21]

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