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Original article

Vulnerability to diabetes in Chinese: an age–period–cohort analysis

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ABSTRACT

Purpose: Hong Kong, in common with other Asian settings, has high rates of diabetes mellitus (DM) despite a relatively nonobese population. Given the rapid economic development in the region, most Asians grew up in limited living conditions. We examined the longitudinal mortality trends of DM. We assessed whether the first generation (birth cohorts in the 1930s) with late adolescence in a more economically developed environment had a lower risk of DM.
Methods: We used DM deaths and population figures in Hong Kong, 1976 to 2010. We fitted age–period–cohort models to decompose mortality rates into effects for age at mortality, calendar period of mortality, and birth cohort.
Results: The risk of death from DM fell for the first generation (births in the early 1930s) with late adolescence in Hong Kong, but possibly the risk rose again for the first generation (birth 1960s) affected by the obesity epidemic.
Conclusions: Adiposity might contribute to diabetes in Hong Kong, and similar Asian settings, however current vulnerability of many older Asians to DM in plentiful environments may be the result of limited living conditions until adulthood. Furthermore, our findings are more consistent with limited adolescent conditions than fetal undernutrition playing a role in vulnerability to DM.

Introduction

Diabetes mellitus (DM) has become a major public health problem in China [1]. As with all noncommunicable chronic diseases, rising DM rates in China represent an interplay of genetic, early life, lifestyle, and environmental factors, whose specific elucidation would facilitate prevention. Asian populations have higher prevalence of DM at a lower body mass index than populations of European descent, which is usually thought to be due to factors such as fetal undernutrition or greater visceral adiposity [2]. In relation to this line of enquiry, the Barker hypothesis states that conditions during pregnancy and the poor nutrition in infancy have long-term effects on health and associated risk of lifelong diseases in adulthood including DM [3]. The Barker hypothesis is immensely appealing, but remains controversial, because it is best supported by observational evidence from developed Western populations and generalizes less well to the rest of the global population, where suitable data to test it is sparse. Experimental tests of the Barker hypothesis in humans have not generally been attempted, evidence from natural experiments is difficult to interpret and sometime hotly contested [4]. Moreover, in developed Western populations, the current issue is over not undernutrition. Reasons for greater susceptibility to visceral adiposity in Asian populations are also not known, nor is the causal pathway from visceral adiposity to DM clear, as surgical removal of specifically visceral fat does not affect glucose metabolism [5]. Other potential drivers of DM consistent with the same observation of greater vulnerability to DM at lower body mass index in Asians, such as lower muscle mass [6], which is a sink for glucose disposal, are rarely considered. Experimental evidence from randomized controlled trials shows that increasing muscle mass through exercise or through testosterone administration improves glucose metabolism [7,8], consistent with some observational evidence [9]. Peak lifetime muscle mass is acquired in adolescence. Currently, most Asian adults grew up in much more limited living conditions than people of European descent in Europe or North America [10].

Hong Kong provides an ideal quasiexperimental setting where the explanatory power of these competing hypotheses can be examined. Hong Kong is a developed non-Western setting with a

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standard of living and social infrastructure similar to North America or Western Europe. Uniquely, the Chinese population of Hong Kong (>95%) experienced a step change in living conditions at a defined time (1945–1955) through migration, of mainly young people looking for work, from the neighboring province of preindustrial China to comparatively economically developed Hong Kong, where the gross domestic product per head in 1950 was about five times higher than in China [10,11]. With subsequent rapid economic growth in Hong Kong [12], childhood obesity began to emerge for early 1960s' cohorts [13]. Thus different generations in Hong Kong experienced markedly improved living conditions at different ages. The early 1930s birth cohorts were the first generation with late adolescence in the more economically developed environment of Hong Kong, with gross domestic product per head of $2218 in 1950 (1990 international dollars), than in preindustrial China, with gross domestic product per head of $439 in 1950 similar to that over the previous 1000 years [10]. Hence, the early 1930s generation had potentially greater peak muscle mass compared with earlier generations. In contrast, the late 1940s birth cohorts were the first generation *in utero* in a substantially more economically developed environment and hence with potentially more plentiful maternal nutrition. The early 1960s birth cohorts were the first generation to experience childhood obesity. Experiences common to specific generation born at the same time with similar experiences, such as markedly better living conditions at a sensitive period during growth and development, would be expected to generate a cohort effect. On the other hand, an exposure, such as the introduction of a new treatment for diabetes would affect everybody at the same time and so would be expected to generate a period effect. Here, we used age–period–cohort (APC) modeling [14] to decompose DM mortality rates into the contribution of age at mortality, calendar period of mortality, and birth cohort effects to identify when changes by cohort occurred and thus distinguish between these hypotheses.

Methods

Sources of data

We obtained the number of registered deaths from type I and II DM (*International Classification of Diseases* (ICD)-8 250, ICD-9 250, ICD-10 E10, E11, E14) and midyear population figures for 1976 to 2010 from the Hong Kong Death Registry and the Census and Statistics Department, respectively. We did not include DM deaths in pregnancy. The Hong Kong Death Registry is a population-based registry covering the registered deaths in the respective years for the entire local resident population. We included all the DM-related deaths during the period of observation in the analysis. We grouped the deaths and population figures into 11 5-year age groups from 35 to 39 to 85+ years, and seven 5-year calendar time periods from 1976 to 1980 to 2006–2010, giving 17 birth cohorts centered at 10-year intervals beginning in 1891.

Statistical analysis

We modeled DM deaths using Poisson APC models [14] with the second period (1981–1985), penultimate period (2001–2005), and the ninth birth cohort (1927–1935) as the reference categories to obtain independent effects of age at death, period at death, and cohort. We put no constraints on the age effects, but we constrained both cohort and period effects to be relative to the reference years. We have previously applied the modeling framework to study secular trends for chronic diseases [12,13,15]. A similar approach regarding the choice of reference categories were adopted previously [13,15,16]. Because of the identifiability problem of APC models [14], only second-order changes (i.e., in slopes or inflection points) of the APC are interpretable. We assessed whether these second-order changes coincided with the timing of defined macro environmental events during economic transition for the Hong Kong population over last century [12,15]. Inflection points in the cohort effects indicate where changes between generations occur. Because of Hong Kong's well-defined and unique population history, large improvement in living conditions at specific ages occurred for the aforementioned cohorts, specifically in late adolescence for the cohorts born in the late 1930s and *in utero* for the cohorts born in the late 1940s. Childhood obesity first occurred for the cohorts born in the 1960s.

We used a "traditional" APC model rather than an intrinsic estimator or hierarchical APC model [17,18]. All APC models require stringent assumptions because of the dependence of cohort on age and period [19]. Assumptions of the traditional APC model are best understood and most relevant to our purpose because we wanted to identify whether inflections occurred for specific birth cohorts [20,21], whereas assumptions of other methods are less clear [22,23].

Bayesian inference was used to estimate model parameter estimates and derived rates summarized as posterior means and 95% credible intervals. In the model, we specified second-order Gaussian autoregressive priors in the forward direction for the age, period, and cohort effects [24], as applied previously [24–26]. These priors specified that the initial expected value of each effect was based on an extrapolation from its two immediate predecessors (i.e., by making an assumption of '*a priori*' belief in smoothness). This would cope with both increasing and decreasing trends [24]. We estimated the model parameters using Markov Chain Monte Carlo simulations with five concurrent chains started at different initial values because comparison of multiple chains can allow us to discern convergence. We used the criteria R-hat to monitor convergence [24]. Based on the values of R-hat, we discarded the first 10,000 samples as a burn-in period and then took a further 40,000 samples from the posterior distributions.

The model goodness-of-fit was measured by the posterior mean deviance, $\overline{D}$ [27]. To compare models, the deviance information criterion (DIC) was calculated, which adjusts the posterior mean deviance for the number of parameters in the model [27]. A smaller DIC implies a better fit. To examine whether the trends differed by sex, we looked for any potential difference in age, cohort, or period effects in men or women by including sex–cohort and/or sex–age and/or sex–period interactions, with assessment of the model fit using the DICs.

All analyses were implemented using R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

Results

Age-standardized mortality rates due to DM from 1976 to 2010

Figure 1 shows the age-standardized annual DM mortality rates per 100,000 people from 1976 to 2010. Age-standardized annual DM mortality rates in Hong Kong fell from 7.9 per 100,000 in 1975 to 4.2 per 100,000 in 2010. Appendix Figure 1 gives a preliminary analysis showing mortality rates by age group and birth cohort.

Age, birth cohort, and period effects for trends in DM mortality

We estimated partial and full APC models and compared different models in terms of DICs. The full model provided the best fit with the smallest DIC compared with the other partial models (Appendix Table 1). The estimated parameter values of age (black