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Dietary exposure to polychlorinated biphenyls and risk of myocardial infarction in men — A population-based prospective cohort study

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ABSTRACT

Background: Major food contaminants such as polychlorinated biphenyls (PCBs) are proposed to play a role in the etiology of cardiovascular disease (CVD), but to date the impact of PCBs on cardiovascular health need to be explored.

Methods and results: We assessed the association between validated food frequency questionnaire-based estimates of dietary PCB exposure and risk of myocardial infarction, ascertained through register-linkage, among 36,759 men from the population-based Swedish Cohort of Men, free of cardiovascular disease, diabetes and cancer at baseline (1997). Relative risks were adjusted for known cardiovascular risk factors, long-chain omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids) and methyl mercury exposure. During 12 years of follow-up (433,243 person-years), we ascertained 3005 incident cases of myocardial infarction (654 fatal). Compared with the lowest quintile of dietary PCB exposure (median 113 ng/day), men in the highest quintile (median 436 ng/day) had multivariable-adjusted relative risks of 1.74 (95% confidence interval [CI], 1.30–2.33; p-trend < 0.001) for total and 1.97 (95% CI 1.42–2.75; p-trend < 0.001) for non-fatal myocardial infarction. In mutually adjusted models, dietary PCB exposure was associated with an increased risk of myocardial infarction, while the intake of long-chain omega-3 fish fatty acids was associated with a decreased risk. We also observed an effect modification by adiposity on the association between of dietary PCB exposure and myocardial infarction, with higher risk among lean men (p value for interaction = 0.03).

Conclusions: Exposure to PCBs via diet was associated with increased risk of myocardial infarction in men.

1. Introduction

Persistent organic pollutants such as polychlorinated biphenyls (PCBs) are major food contaminants that are proposed to play a role in the etiology of cardiovascular disease (CVD) (Humblet et al., 2008). Fish is the main dietary source of exposure to these bio-accumulating pollutants (Meharg & Osborn, 1995; Liem et al., 2000; Bergkvist et al., 2012) and to methylmercury (MeHg) (Wennberg et al., 2012; Mozaffarian et al., 2011a). Importantly, fish is also the main source of various essential nutrients, including long-chain omega-3 fatty acids (i.e., eicosapentaenoic acid and docosahexaenoic acid; EPA and DHA). In the absence of randomized trials on fish consumption, the evidence of the beneficial effects on coronary heart disease incidence and mortality comes from observational and experimental studies (Mozaffarian et al., 2011b; Mozaffarian & Rimm, 2006; Lajous et al., 2013), while EPA and DHA randomized supplementation trials show no clear protection (Rizos et al., 2012). Aspects of benefits and risks of fish consumption have high public health relevance.

PCBs are fat-soluble chemicals that remain in the body for extended periods of time (Milbrath et al., 2009). Although a lower total body burden is observed in lean as compared to obese individuals, the body concentration is higher in lean individuals (Glynn et al., 2003). Experimental studies indicate that PCBs cause endothelial cell dysfunction, hyperlipidemia and hypertension, which are corner stones in the development of atherosclerosis (Felty et al., 2010; Helyar et al., 2009; Hennig et al., 2005a; Jokinen et al., 2003; Lind et al., 2004; Toborek et al., 1995; Hennig et al., 2002). In humans, PCB exposure has been associated with several intermediate risk factors for CVD such as hypertension (Ha et al., 2009; Kreiss et al., 1981; Goncharov et al., 2011; Everett et al., 2008; Donat-Vargas et al., 2015), hyperlipidemia (Kreiss et al., 1981; Lee et al., 2011; Goncharov et al., 2008), atherosclerosis (Pines et al., 1986; Lind et al., 2011), metabolic syndrome (Lee et al., 2007), and type 2 diabetes (Lee et al., 2010; Everett et al., 2011). To date, only few prospective epidemiological studies have explored the association with clinical CVD (Bergkvist et al., 2014; Gustavsson & Hogstedt, 1997; Bergkvist et al., 2015; Lee et al., 2012; Kim et al., 2015).

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The aim of the present study was to assess the association between validated estimates of dietary PCB exposure and risk of myocardial infarction in a large population-based prospective cohort of middle-aged and elderly men, taking into account the intake of EPA, DHA and MeHg exposure and a possible modifying effect of adiposity.

2. Methods

2.1. Population

The Cohort of Swedish Men was initiated in 1997 when men aged 45–79 years and residing in the central part of Sweden (Västmanland and Örebro counties), received a 350-item questionnaire that included diet and other lifestyle factors (response rate 49%). Of the 48,850 men who returned a completed questionnaire, we excluded those with an erroneous or a missing national identification number (Supplemental Fig. 1). We further excluded men from the baseline population with prevalent cardiovascular disease including myocardial infarction, angina and stroke (identified through the National Hospital Discharge Register), malignant neoplasms (identified through the Swedish Cancer Register), diabetes (self-reported and identified through linkage with the National Hospital Discharge Register and the National Diabetes Register), and those with implausible values for total energy intake (i.e., 3 standard deviations from the $\log_e$-transformed mean energy intake). The final study population consisted of 36,759 men at the start of follow-up. The study was approved by the Regional Ethical Review Board at the Karolinska Institutet (Stockholm, Sweden).

2.2. Assessment of dietary PCB exposure and other covariates

The self-administered questionnaire included questions on the habitual diet, education, body weight, height, waist circumference, history of smoking, physical activity, history of certain diseases and use of supplements and certain medications. Questions on diet consisted of a 96-item food frequency questionnaire (FFQ) reflecting the men's average consumption of different foods and beverages during the last year. The FFQ was based on open-ended questions with pre-specified serving sizes for frequently consumed foods (e.g., dairy products), and eight predefined frequency categories ranging from never to ≥3 times per day for other foods.

The dietary exposure to PCBs and MeHg was estimated through recipe-based databases created for the FFQ. The PCB-database, described in detail elsewhere (Bergkvist et al., 2012), was based on concentrations of the PCB congener 153 (in total there are 209 congeners) at the time of baseline. PCB congener 153 is the most abundant congener in food on the Swedish market and levels of PCB 153 is an excellent indicator for total PCB levels in food as well as in human blood serum (Glynn et al., 2003; Atuma et al., 1996; Covaci et al., 2002; Glynn et al., 2000). PCBs are bioaccumulating, fat-soluble compounds that are mainly found in food of animal origin, whereas fruits and vegetables usually contain lower levels. Fatty fish from contaminated waters can contain particular high levels of PCBs (Bergkvist et al., 2012). The content of PCB and MeHg in foods was obtained from the Swedish Environmental Protection Agency (Strom et al., 2011) and the Swedish National Food Agency (Atuma et al., 1996; Glynn et al., 2000; Lignell et al., 2009; Glynn et al., 2009), which also provided food contents of EPA, DHA and saturated fatty acids and are considered to be representative. Dietary exposure to PCB153 and MeHg and the intake of fatty acids were estimated by multiplying the average concentration in various foods with the respective consumption frequency and age-specific portion-size, and were finally adjusted for total energy intake using the residual-regression method (Willett & Stampfer, 1986). The FFQ-based dietary PCB estimates have been extensively validated against serum PCBs in women (56–85 years of age) from the Swedish Mammography cohort — a population-based cohort from the same area in Sweden as the COSM. The correlation coefficient (r) between the sum of six abundant PCB congeners in serum (CB-118, 138, 153, 156, 170, 180) and estimated long-term dietary PCB exposure assessment (estimated twice up to 9 years prior to blood sampling) ranged from 0.3 to 0.6 (p values < 0.05) (Bergkvist et al., 2012). Fish consumption, the main source of MeHg exposure, correlates well with hair and blood mercury in Swedish populations (r ≥ 0.7) (Strom et al., 2011). FFQ-based dietary intakes of EPA and DHA have been validated against fourteen 24-h recall interviews (r = 0.6 for both) in 248 men (40–74 years of age) from the study area (Messerer et al., 2004), and against adipose tissue levels (r = 0.5 and 0.4, respectively) in women from the study area (Wolk et al., 1998). From the FFQ, we also obtained data on consumption of fruit, vegetables, dairy products and red and processed meat, possibly affecting the risk of myocardial infarction (Mozaffarian et al., 2011b). Total daily physical activity was assessed and expressed as metabolic equivalents (METs) with the use of a validated questionnaire (Orsini et al., 2008).

2.3. Case ascertainment of myocardial infarction

Incident cases of myocardial infarction were ascertained through computerized linkage via the personal identification number to the Swedish National Hospital Discharge Register and the Cause of Death Register. We used the International Classification of Disease, 10th Revision code I21 for myocardial infarction, and fatal events were defined as death within 28 days from first diagnosis. The registries for myocardial infarction are considered almost complete (Hammar et al., 2001).

2.4. Statistical analysis

Men were followed from January 1, 1998 and censored at date of first myocardial infarction, death (National Death Register) or end of follow-up (31 December 2010), whichever occurred first. We categorized men into quintiles of dietary PCB exposure at baseline. Cox proportional hazards regression models with attained age (in years) as the underlying timescale were used to estimate hazard ratios, hereafter referred to as relative risks (RR), with 95% CIs. In the multivariable-adjusted analysis, we adjusted for level of education, family history of myocardial infarction before 60 years of age, high cholesterol, hypertension, use of aspirin, smoking status, waist circumference, total physical activity, use of fish oil supplements, alcohol consumption, energy intake, consumption of fruit and vegetables, dairy products and red and processed meat, dietary intake of saturated fatty acids and dietary MeHg exposure. In additional adjustments, we added the dietary intake of sum of EPA and DHA. The Schoenfeld's residual test showed no indications of violation of the proportional hazard assumption. Linear trend across categories was tested using median values of dietary PCB or EPA and DHA within categories as a continuous variable. To elucidate the effect of potential collinearity between PCB and EPA and DHA, we performed analyses stratified by high and low EPA and DHA intake based on tertiles of dietary PCB exposure, because of few persons with opposing exposures. To test for possible interactions, the likelihood ratio test was used to compare models with and without an interaction term of dietary PCB quintiles and waist circumference (<102, ≥102 cm). To examine a potential nonlinear dose–response relationship, we modeled PCB exposure and EPA and DHA intake using restricted cubic splines with five knots at the median values of quintiles. (Orsini & Greenland, 2011) All statistical analyses were performed in Stata (Intercooled Stata software version 12; StataCorp, LP). Reported p values were from two-sided statistical tests where a p value of <0.05 was considered statistically significant.

3. Results

During 12 years (433,243 person-years) of follow-up, we ascertained 3005 incident cases of myocardial infarction of which 2351 were non-fatal. Mean dietary exposure to PCBs (i.e. PCB153) was