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Paternal occupational lead exposure and offspring risks for schizophrenia

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ABSTRACT

This register-based cohort study investigated whether paternal occupational exposure to inorganic lead was related to offspring risk for schizophrenia spectrum disorder (SSD). Exposed men ($n = 11,863$) were identified from blood lead measurements taken at the Finnish Institute of Occupational Health in 1973–1983. Data on mothers and their offspring born from 1972–1984 were obtained from the national Population Information System. Two population comparison offspring for each exposed offspring were matched on date of birth, sex and area ($n = 23,720$). SSD cases were identified from The Finnish Hospital Discharge Register. Hazard ratios of SSD between exposed groups were analyzed using conditional proportional hazards regression, adjusted for parental history of psychoses, parental ages, language of offspring, father's employment, and father's self-employment. After 26–38 years of follow up, there were no significant differences in the incidence of schizophrenia, either between the offspring of exposed (188/11,863; 1.6%) and unexposed fathers (347/23,720; 1.5%) or based on blood lead levels (adjusted hazard ratios (aHR): 0.97, CI 0.52–1.83, 1.25, CI 0.85–1.82, 0.90, CI 0.54–1.49, and 1.38, CI 0.65–2.92 for lead categories <0.5, 0.5–0.9, 1.0–1.4, and ≥1.5 μmol/L, respectively, as compared to population comparison). Parental psychosis, paternal age and offspring language were associated with offspring risk. The findings suggest that paternal exposure to lead is not a risk factor for schizophrenia in offspring. However, the majority of exposed fathers had low-level exposure, and we cannot exclude the possibility of an effect for higher exposures to lead.

1. Introduction

The role of prenatal exposures as risk factors for schizophrenia is well established, including maternal stress, nutritional deprivation, and infections (reviewed by Brown, 2011). Exogenous toxins may also be relevant, based on findings on increased risks for schizophrenia in association with high maternal third trimester serum lead levels (Opler et al., 2008) and parental occupation in dry cleaning (Perrin et al., 2007). The latter study suggests that toxic exposures of the paternal germ line may also be important for offspring risk. The paternal germ line is highly mutable, which is relevant to the association of advancing paternal age and increasing schizophrenia risks in offspring (Kranz et al., 2015; Kong et al., 2012; McGrath et al., 2014; Milekic et al., 2015). No study has yet primarily examined if paternal lead exposure prior to conception is related to offspring schizophrenia risk.

Lead (Pb) is a common occupational exposure (Kauppinen et al., 2000) with known toxicity to male reproductive health (e.g. Apostoli et al., 1998). Blood lead concentrations >1.9 μmol/L are detrimental to semen quality (Apostoli et al., 1998) and lead salts were historically used as spermicides. During the 1960s and 1970s, the acute and chronic effects of Pb exposure on male fertility became a concern for occupational health and safety (Anttila, 1994). Male lead exposure was linked in some studies to prolonged time to pregnancy, reduced fertility rate and adverse pregnancy outcomes (reviewed by Bellinger, 2005, Taskinen et al., 2011).

The current investigation tested the hypothesis that paternal occupational exposure to lead would increase the risk of schizophrenia in the offspring. This study utilized data on paternal blood lead exposure measurements collected at the Finnish Institute of Occupational Health in 1973–83.

2. Materials and methods

2.1. Study population

This cohort study compared the offspring of men who were biologically monitored for occupational exposure to lead (1973–1983) to a

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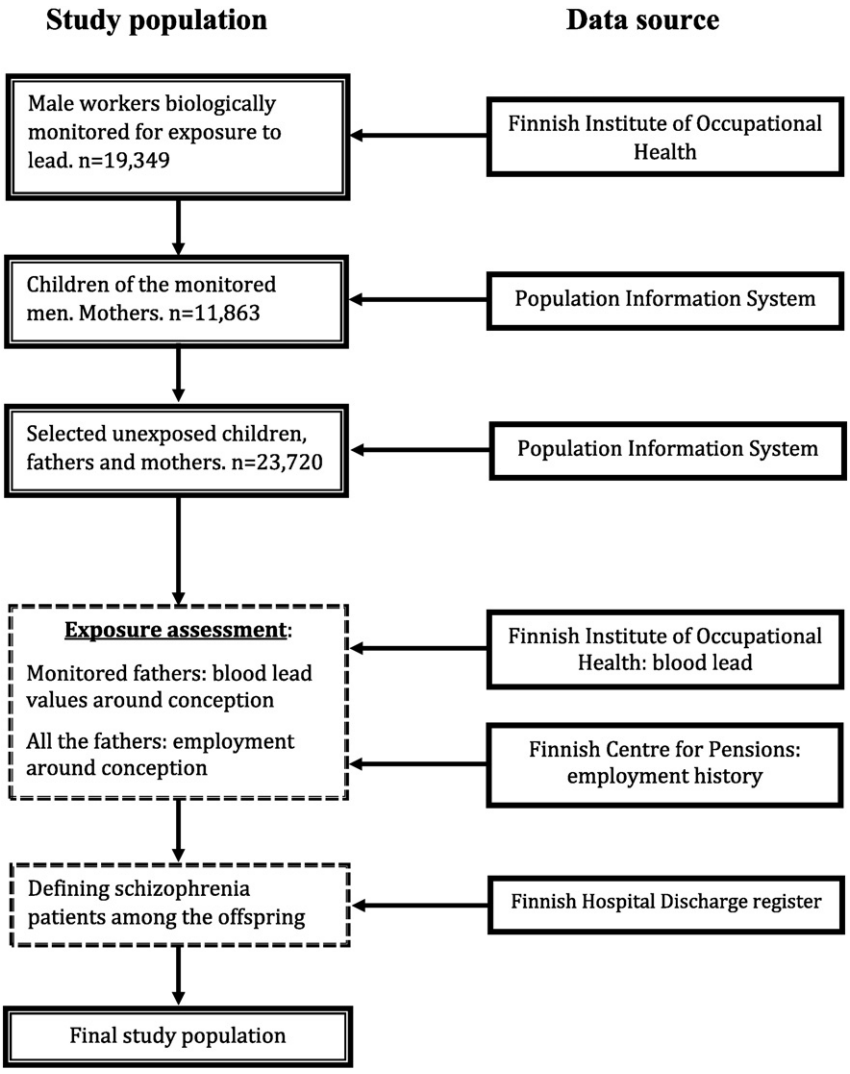

Fig. 1. Identification of the study population and register data sources used in the study.

matched sample of the Finnish population (born in 1972–1984) as to schizophrenia risk, also examining risks with respect to the monitored blood lead levels (Fig. 1).

The children of the monitored men and mothers of the children were identified from the Population Information System maintained by the Population Register Centre. The total number of children was 34,738, of which 12,070 children born in 1972–1984, years of the blood lead measurements. Excluded offspring had prohibited disclosure ($n = 11$), unknown place of birth ($n = 36$), born abroad ($n = 149$), and spoke a language other than Finnish or Swedish ($n = 11$). The 7427 fathers produced 11,863 children in the study group. Two population comparison offspring and parents, unrelated to the monitored men, were identified from the Population Information System, matched for place of birth, sex, and the date of birth, yielding 23,720 comparison offspring, with 6 cases in which only one population control was available.

2.2. Exposure data

The cohort of biologically monitored workers (Anttila, 1994, Anttila et al., 1995) includes personal identification codes (ID), sex, measurement date and blood lead (PbB). Altogether 56,117 measurements have been conducted for 19,349 men, most having one measurement. According to the Finnish Act of Labor Protection (299/58), if the PbB of any worker at the workplace exceeds 1.9 μmol/L (40 μg/dL), all the workers in similar work tasks should be monitored 1–6 times a year, and virtually all the workers in Finland exposed at that level have been monitored. For most of the workplaces with lower exposure levels the analyses were conducted based on the initiative of employers. The ID was available for 97% of our measurements. The most exposing industries were lead smelting, metal scrap business, metal foundries, railroad equipment machine shop, painting enterprises, manufacture of glass, storage battery factories, motor car repair shops, and ammunition manufacture (Anttila, 1994). Both blood lead levels and numbers of monitored workers were clearly higher in men than in women.

2.3. Exposure assessment

Registered information on date of birth (Population Information System) and employment history (Finnish Centre for Pensions) were used to assess employment status of all exposed and unexposed fathers for the time of the assumed 80-day preconceptional spermatogenesis period. Among fathers biologically monitored for exposure to lead, men holding the job of measurement around the time of spermatogenesis were defined as *exposed* fathers and their children as exposed children ($n = 6875$). Fathers monitored for exposure to lead but not from the job held at that time period were considered *potentially exposed* and analyzed as a separate group ($n = 4988$ children). As only about 1% of the Finnish workforce was exposed to lead in 1980s (Anttila, 1994) comparison fathers were considered to constitute the *external unexposed group*