

## METHODS SECTION

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## METHODS

## Study Participants

The DNBC was established in Denmark during 1996–2002, when 100,418 pregnant women enrolled in the cohort at their first general-practitioner antenatal visit (during weeks 6–12), and the mothers and children have been followed since (33). For analyses of prenatal acetaminophen use, we restricted the cohort to live-born children whose mothers answered the study enrollment form and the 3 subsequent telephone interviews (scheduled at approximately the 12th and 30th gestational weeks and at 6 months after birth), all of which collected information on prenatal acetaminophen use ( $n = 64,322$ ). Among them, 40,934 had SDQ outcome scores reported by both the mother and the child when the index child was 11 years old. For postnatal acetaminophen exposure analyses, we additionally restricted the cohort to mothers who had answered the interview conducted at 18 months after birth with information on the infant's acetaminophen treatment ( $n = 27,742$ ). Details in the study population selection are described in Web Figure 1 (available at <https://doi.org/10.1093/aje/kwaa257>). All participants provided written informed consent at the time of inclusion in the DNBC. The research protocol for this study was approved by the DNBC steering committee (project no.: 2018–13), Danish data inspectorate (journal no.: 2016–051-000001, serial no.: 1297), and the institutional review boards at the University of California, Los Angeles (16–001849), and Yale University (2000024089).

Methods section is clearly defined and has subsections which describe *study data*, *exposure* definition, and *outcome* assessment.

Describe data setting, timeframe, and N participants, and other relevant info (gender, age of participants)

Describe any exclusions from the dataset and *why*.

Add human subjects statement—necessary for publication in many journals.

## Exposures to acetaminophen

Information about maternal acetaminophen use during pregnancy was ascertained from the study enrollment form and 3 computer-assisted telephone interviews. At the first contact, women answered questions regarding any supplement and medication use covering the period from 4 weeks before pregnancy to the gestational week of reporting. In the subsequent telephone interviews, women were specifically asked to report whether they had taken any painkillers during pregnancy and provided with a list of 44 common medica-

Clearly define how exposure information was collected.

tions, including acetaminophen as a single or combination drug. Women were asked to indicate the gestational week of intake for each medication, and **we used the weekly intake information to calculate trimester-specific and cumulative weeks of use.**

Information regarding acetaminophen exposure during infancy was ascertained through the computer-assisted telephone interviews at about 6 and 18 months postpartum. Mothers were asked to report whether their children had experienced any of 16 types of conditions or diseases and the specific pharmaceutical treatment for these conditions (Web Table 1).

Define how the data was aggregated or analyzed (e.g. any data summations, transformations, standardizations).

### **Parental and self-reports of children's behavioral problems at age 11 years**

Children's behaviors were assessed based on the standard-ized SDQ, **which is a 25-item screening tool that assesses behavioral problems and mental health status of children and adolescents between the ages of 4 and 18 years (34).** When the DNBC children turned 11 years of age, both parents and children were invited to complete the SDQ. There are 5 SDQ subscales (emotional symptoms, conduct problems, hyper-activity/inattention, peer problems, and prosocial behavior), all consisting of 5 items. Based on the recommendations for scoring the SDQ (<http://www.sdqinfo.com>), we calculated a total difficulties score (range, 0–40) by summing the first 4 subscales, **ranging from 0–10 each, with higher scores indicating more negative behaviors and problems. We then dichotomized each subscale according to the recommended cutoff to indicate atypical behaviors for the parent-reported and child-reported SDQ (34).** We also created an “internalizing” subscale, which combined the emotional symptoms and peer problems subscales, and an “externalizing” subscale that combined the cutoff points for internalizing or externalizing composite scores; thus, **the top 95th percentile of each distribution was defined a priori as the cutoff.** A subset of parents also answered 6 questions (each with a possible response value of 0, 1, or 2) about their own behavioral problems during childhood when the index child turned 7 years of age (7), which allowed us to generate a parental behavioral problems score (range 0–12).

Clearly explain the survey tool used. (Assume the reader is unfamiliar with it.)

Explain how to interpret the outcome variables

Clearly define cut-off values for analysis (and why those cut-offs were chosen) and interpretation.