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Heavy prenatal alcohol exposure and overall morbidities: a Danish nationwide cohort study from 1996 to 2018

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Summary

Background Heavy prenatal alcohol exposure is harmful and can lead to fetal alcohol spectrum disorders. A systematic review and meta-analysis identified 428 comorbidities in individuals with fetal alcohol spectrum disorders, and reported pooled prevalence estimates. We aimed to investigate overall risk of morbidities in heavy prenatal alcohol-exposed children by estimating risk of the identified comorbidities, and previously unidentified diseases and health-related problems.

Methods Our Danish nationwide register-based cohort study included all singleton births. Individuals were followed up to age 18 years, between 1996 and 2018. Stillbirths and children of immigrants were not included in the study, and births of women who migrated within 1 year before or during pregnancy were also excluded due to loss to follow-up. Data on health and education were extracted from the Danish Medical Birth Register, the Danish National Patient Registry, the Danish National Prescription Registry, the Danish Civil Registration System, and the Population Education Register. We estimated crude and standardised risk differences of hospital diagnoses. Heavy prenatal alcohol exposure was defined by hospital contacts with alcohol-attributable diagnoses given to the mother or her child, or by maternal redeemed prescriptions for drugs to treat alcohol dependence 1 year before or during pregnancy.

Findings Of 1 407 689 identified singleton births, 219 186 were excluded for reasons including they were born to immigrants, lost to follow-up, or were stillbirths. Of the remaining 1 188 503 children, 4799 (0·4%) had heavy prenatal alcohol exposure and 1 183 704 (99·6%) were classified as non-alcohol-exposed births. 578 179 (48·6%) babies were female and 610 324 (51·4%) were male. We found 234 of 428 previously identified comorbidities in individuals with fetal alcohol spectrum disorder, of which 29 conditions had a standardised risk difference of at least 0·5%, predominantly related to brain function, behavioural disorders, infections, and neonatal conditions. The four highest standardised risk differences were found for low birthweight (4·70% [95% CI 3·70–5·71]), small for gestational age (4·63% [3·72–5·55]), delayed milestone (3·81% [2·99–4·64]), and other preterm infants (2·69% [1·71–3·68]). Of previously unidentified diseases and health-related problems, 32 of 719 had a standardised risk difference of at least 1·0%, mainly related to brain function, some injuries, substance-related conditions, and childhood adversities.

Interpretation Heavy prenatal alcohol exposure is associated with an overall increased risk of child morbidities and previously unrecognised alcohol-related health problems. Prenatal alcohol exposure is a key public health issue with a potential negative impact on child and adolescent health. This study urges for renewed efforts and substantiates the profound degree to which pre-conceptional care is mandatory.

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Introduction

Prenatal alcohol exposure is a global public health threat.[1] Heavy alcohol exposure interferes with normal fetal development[2] and can lead to adverse birth outcomes and fetal alcohol spectrum disorders.[2] Fetal alcohol spectrum disorders is an umbrella term covering a continuum of lifelong disabilities, from mild to severe, with a variety of characteristic dysmorphic facial features, growth restriction, and cognitive and neurobehavioural impairment and malformations.[2] Fetal alcohol syndrome represents the most severe condition of these types of disorders.[2] Furthermore, animal studies report prenatal alcohol exposure to potentially alter development of most organs.[3] These findings have led to the hypothesis that heavy prenatal alcohol exposure plays an important role in the pathophysiology of disease development with subsequent increased risk of conditions in affected individuals.[3] In 2016, Popova and colleagues[4] did a systematic review including a meta-analysis, which identified a total of 428 comorbidities in individuals with

Research in context

Evidence before this study

The characteristics of fetal alcohol syndrome in children born to mothers with alcohol use during pregnancy were first described in the 1970s. Since then, a growing body of research on prenatal alcohol exposure has appeared. Even so, the extent of the effect of alcohol on morbidity among affected individuals is not fully clarified. In 2016, Popova and colleagues published a systematic review including a meta-analysis reviewing studies of comorbidities in individuals with fetal alcohol spectrum disorders. They identified 428 comorbidities, and pooled prevalences were estimated. In the absence of risk estimates of these identified comorbidities, we searched PubMed with no language restrictions for observational studies, systematic reviews and meta-analyses published from Jan 1, 2012, to Dec 19, 2021, for studies concerning fetal alcohol spectrum disorder or prenatal alcohol exposure. The search generated 170 studies. Most of the studies were based on small sample sizes, included few outcomes, had inconsistent results, or concluded that further research was needed.

Added value of this study

This study used nationwide registries to map multiple hospital-related conditions among more than 1·1 million Danish children. Based on recorded confirmed alcohol-attributable conditions and redeemed prescriptions for drugs to treat maternal alcohol dependence, 0·4% children of the Danish population were identified to have heavy prenatal alcohol exposure from 1996 to 2018. Highly relevant potential confounders (eg, maternal psychiatric disease and substance use) were considered in the analyses, adding extra value to our results. Our results provide a unique insight into the disease pattern of heavy prenatal alcohol-exposed children with risk estimates for the previously identified as well as unidentified diseases and health-related problems. Conditions at risk were those related to fetal alcohol spectrum disorders, such as disorders related to fetal growth, epilepsy, and mental and behavioural disorders; and furthermore, preterm birth, infections, some body injuries, and adverse childhood experiences. Some results were in line with the existing literature, others were, to the best of our knowledge, novel findings.

Implications of all the available evidence

The available evidence sheds light on the adverse effect of alcohol on the fetus. This study emphasises that more conditions might be associated with prenatal alcohol exposure than previously assumed. Alcohol consumption during pregnancy is a key public health concern which calls for global attention to protect health among children. Awareness should be directed towards prevention, maternal health, and the potential effects of alcohol exposure in the child, as well as adverse childhood experiences and adversities.

fetal alcohol spectrum disorders. Popova and colleagues thereby presented the first comprehensive list of comorbidities specified by pooled prevalence estimates.[4] Of those, 18 comorbidities were found with a pooled prevalence higher than 50% among individuals with fetal alcohol syndrome.[4] However, only prevalences were provided and the number of identified comorbidities at increased risk remains unknown. We therefore searched PubMed for observational studies and systematic reviews and meta-analyses, published within the past 10 years, concerning fetal alcohol spectrum disorders or prenatal alcohol exposure (appendix p 12). The search generated 170 studies showing conflicting results for some identified conditions. Many of the studies were clinical, based on small sample sizes, and their results have not collectively been further replicated.

See Online for appendix

It has been estimated that 9·8% of women globally expose their pregnancy to any use of alcohol.[1] Although this could be an overestimate, as secular trends of decrease in alcohol consumption among pregnant women were not included in the model, it is still alarming and calls for action, especially as the global prevalence of fetal alcohol spectrum disorders amounts to 7·7 per 1000 people.[1,5]

To extend the work by Popova and colleagues, we did a nationwide cohort study with the aim of estimating (1) risks of the 428 pre-identified comorbidities in individuals with fetal alcohol spectrum disorder;[4] and (2) risks of previously unidentified diseases and health-related problems in heavy prenatal alcohol-exposed children.

Methods

Study design and participants

The publicly funded Danish health-care system has a proactive strategy to identify and prevent morbidity, psychosocial, and behavioural problems, and accidents among children by providing: (1) five home visits from a community nurse within the first year of life; (2) seven preventive health examinations within the first 5 years of life at the general practitioner (the participation rate is more than 93%);[6] and (3) primary school health screenings conducted by community nurses. This nationwide register-based historical cohort study included all Danish children of singleton births from Jan 1, 1996 to Dec 31, 2018. Individuals were followed up until the age of 18 years. Only live births were included and children of immigrants were excluded due to a large proportion of maternal missing data. Births of women who migrated within 1 year before or during pregnancy were also excluded due to loss to follow-up.

All Danish citizens hold a unique, personal civil registration number for administrative usage, which enables individual-level linkage between national registries.[7,8] By such linkage, data on diagnosis codes according to the International Classification of Diseases (ICD)-8 and ICD-10 were obtained from the Danish National Patient Registry, which holds information on hospital admissions since 1977, and any hospital contact since 1995.[9] Data on maternal educational level was obtained from the Population Education Register.[10] Data on maternal ethnicity was based on the parent and child's country of birth and extracted from the Danish Civil Registration System,[8] as were dates of death. Information on redeemed prescriptions from all Danish pharmacies according to the Anatomical Therapeutic Chemical codes was obtained from The Danish Prescription Registry.[11] We collected data on date of birth, gestational age, child sex, birthweight, parity, and maternal age at birth from the Danish Medical Birth Register.[12] Missing data on gestational age was replaced with 40 weeks' gestation. The Danish registries have been validated, previously described in detail, and are generally of high quality and completeness.[7]

In accordance with the General Data Protection Regulation, approval to use data sources for research purposes was granted by the data responsible institute in the Capital Region of Denmark (approval number: P-2019–280). In Denmark, ethical committee approval or patient consent are not required for register-based studies.

Procedures

As a proxy measure for heavy prenatal alcohol exposure, we used clinically recognised conditions, by definition, caused directly by alcohol use and alcohol treatment, defined as the presence of at least one of the following criteria: (1) maternal hospital contacts with a 100% alcohol-attributable diagnosis within 1 year before or during the pregnancy; (2) redeemed prescription for drugs to treat maternal alcohol dependence within 1 year before or during pregnancy; and (3) a prenatal alcohol-related diagnosis given to the child (appendix p 12). The 100% alcohol-attributable diagnoses include acute and chronic conditions according to pre-existing lists.[13,14] Pregnant women were screened for alcohol use at the first antenatal care visit and referred to hospital in case of excessive use. As pre-pregnancy drinking is strongly associated with drinking during pregnancy, we included one year of exposure before the index pregnancy.[15] Danish antenatal care provides free ultrasound pregnancy dating.[16] Pregnancy start was calculated by subtracting gestational age at birth from date of birth, equivalent to the (theoretical) first day of the last menstrual period.

Outcomes of interest were overall morbidities in heavy prenatal alcohol-exposed children. In primary analyses, we investigated 428 pre-identified conditions in individuals with fetal alcohol spectrum disorders reported by Popova and colleagues.[4] In secondary analyses, we investigated diseases and health-related problems not included in the primary analyses. All outcomes were assessed in all patients with available data. For statistical reasons, outcomes were divided into three groups according to the time of onset: (1) During pregnancy or at birth (ie, ICD-10 chapter XVII ''Congenital malformations, deformation and chromosomal abnormalities'' (Q00-Q99), ICD-10 blocks of ''Fetus and newborn affected by maternal factors and by complications of pregnancy, labour and delivery'' (P00-P04*), ''Disorders related to length of gestation and fetal growth (P05-P08), and birth trauma'' (P10-P15). (2) Newborn (ie, ICD-10 chapter XVI ''Certain conditions originating in the perinatal period'' (P20-P96). (3) Childhood (ie, all other conditions with the exception of ICD-10 chapter XXll ''Codes for special purposes'' and XXI ''Factors influencing health status and contact with health services'', including only the following subgroups and blocks; Z03, Z07, Z6, and Z8. ''Disorders related to length of gestation and fetal growth'' (P05-P08) were evaluated as composite outcomes defined by respective ICD-10 codes and register information on birthweight and gestational age. ''Small for gestational age'' was defined as birthweight of more than 2 SD below the mean for gestational age, between 25+0–42+6 weeks, according to Marsál's growth curves.[17] Outliers defined as +/– 4 SD from the mean were excluded.

Statistical analysis

Maternal chronic somatic disease was defined by prevalent chronic conditions in Danish pregnant women reported by Jølving and colleagues[18] within 10 years before giving birth (appendix p 13). Maternal psychiatric disease was defined as a condition within the ICD-10 (chapter V, mental and behavioural disorders [F20-F99] within 2 years before birth or mental disorders complicating pregnancy, childbirth and the puerperium [O99.3B]). Prenatal exposure to substance use was defined by substance-attributable diagnoses given to either the newborn or the mother within 1 year before or during pregnancy (appendix p 14). We used maternal highest achieved educational level at birth as a proxy for socioeconomic status, categorised into four levels according to the International Standard Classification of Education (ISCED;[19] appendix p 14). Women with non-registered educational information were categorised as having primary and lower secondary education. Parity was categorised as 0, 1, and 2 or more according to status before the index birth. Missing data on parity was replaced with birth count of the mother before the index birth recorded in the Danish Medical Birth Register (1996 onwards).

Maternal characteristics are presented as counts with percentages. The outcomes were grouped according to the time of assessment: during pregnancy or at birth,

	Total (n=1 188 503)	Reference group (n=1 183 704)	Heavy prenatal alcohol exposed (n=4799)
Sex			
Female	578 179 (48·6%)	575 862 (48·6%)	2317 (48·3%)
Male	610 324 (51·4%)	607 842 (51·4%)	2482 (51·7%)
Maternal age, years			
13–20	29 217 (2·5%)	28 404 (2·4%)	813 (16·9%)
21–30	625 760 (52·7%)	623 362 (52·7%)	2398 (50·0%)
31–40	515 730 (43·4%)	514 248 (43·4%)	1482 (30·9%)
41–61	17 796 (1·5%)	17 690 (1·5%)	106 (2·2%)
Parity			
Nulliparous	546 525 (46·0%)	543 608 (45·9%)	2917 (60·8%)
Parous (1)	443 585 (37·3%)	442 612 (37·4%)	973 (20·3%)
Parous (>1)	198 393 (16·7%)	197 484 (16·7%)	909 (18·9%)
Maternal chronic somatic disease*	133 070 (11·2%)	132 154 (11·2%)	916 (19·1%)
Maternal psychiatric disease†	116 189 (9·8%)	113 800 (9·6%)	2389 (49·8%)
Maternal substance use‡	5269 (0·4%)	4212 (0·4%)	1057 (22·0%)
ISCED			
Primary and lower secondary	210 724 (17·7%)	207 646 (17·5%)	3078 (64·1%)
Upper secondary	485 349 (40·8%)	484 075 (40·9%)	1274 (26·5%)
Short cycle tertiary and Bachelor's or equivalent	356 369 (30·0%)	356 010 (30·1%)	359 (7·5%)
Master's or equivalent and doctoral or equivalent	136 061 (11·4%)	135 973 (11·5%)	88 (1·8%)
Infant death	5594 (0·5%)	5543 (0·5%)	51 (1·1%)

Data are n (%). ISCED=International Standard Classification of Education. *Maternal chronic somatic disease was registered within 10 years before birth. †Maternal psychiatric disease was registered within 2 years before birth. ‡Maternal substance use was registered within 1 year before or during pregnancy.

Table: **Baseline characteristics**

within 1 year (newborn outcomes), or within 18 years of age (childhood outcomes). For the analyses of newborn and childhood outcomes, children were followed up from birth until outcome occurrence, death without outcome (competing risk), or end of follow-up, whichever came first. We estimated the differences in the absolute outcome risks between children with the exposure versus without the exposure. In the crude analyses, the Aalen-Johansen method was used.[20] In the standardised analyses, we used inverse probability weighting to deal with censoring and competing risks,[21] and applied generalised random forests to standardise the distribution of the covariates.[22] By use of the random forest approach, we circumvented the need to specify semi-parametric regression models, and implicitly allowed for interactions and non-linear effects of the covariates. Because our main interest is in the group of exposed children, all reported standardised risk differences were standardised to the distribution of the following covariates among the heavy prenatal alcohol-exposed children: sex, maternal age, parity, maternal chronic somatic disease and psychiatric disease, prenatal exposure to substance use, and maternal educational level at birth. Confidence intervals were estimated using the entire sample of exposed children and a subsample of 300 000 observations of the reference group. As a sensitivity analysis, we estimated standard risk differences in two subsets of children according to exposure: (1) chronic alcohol-attributable conditions diagnosed in the mother or her child, or prescriptions for drugs to treat maternal alcohol dependence; and (2) 100% acute alcohol-attributable conditions diagnosed in the mother. R software (version 3.6.1) was used for all analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

1 407 689 singleton births were identified from the Danish Birth Medical Register, and 219 186 were excluded as they were stillbirths, lost to follow-up, had ISCED not elsewhere classified, or were born to immigrants that had up to 80% of maternal missing data. Of the 1 188 503 liveborn singleton births eligible for inclusion, 4799 (0·4%) were recognised as heavy prenatal alcohol-exposed and 1 183 704 (99·6%) were classified as non-alcohol-exposed births (appendix p 2). Missing data for parity was 1·8% and for gestational age was 2·6% before replaced values. 578 179 (48·6%) of births were female and 610 324 (51·4%) were male. Gender data were obtained from the Danish Medical Birth Register, recorded at birth. The median potential follow-up time was 10·6 years in the alcohol-exposed group versus 11·8 years in the reference group. Early end of follow-up occurred mainly due to late inclusion into the study population (eg, a child born in 2005 could not be followed up until age 18 years). Compared with the reference group, alcohol-exposed children had a higher mortality (51 [1·1%] of 4799 *vs* 5543 [0·5%] of 1 183 704) and were more often prenatally exposed to substance use (1057 [22·0%] of 4799 *vs* 4212 [0·4%] of 1 183 704). Furthermore, alcohol-exposed children more often had mothers younger than 20 years at delivery (813 [16·9%] of 4799 *vs* 28 404 [2·4%] of 1 183 704), who were nulliparous (2917 [60·8%] of 4799 *vs* 543 608 [45·9%] of 1 183 704), had a chronic somatic disease (916 [19·1%] of 4799 *vs* 132 154 [11·2%] of 1 183 704) or psychiatric disease (2389 [49·8%] of 4799 *vs* 113 800 [9·6%] of 1 183 704), and had the lowest educational level (3078 [64·1%] of 4799 *vs* 207 646 [17·5%] of 1 183 704; table).

Of 428 pre-identified prevalent comorbidities in individuals with fetal alcohol spectrum disorder,[4] we identified 357 conditions in our study population, and 234 conditions in the heavy prenatal alcohol-exposed children. Absolute risks for the 357 conditions and crude and standardised risk differences for the 234 conditions are summarised in the appendix (pp 15, 41). In total, 133 conditions occurred in five or more alcohol-exposed children (ie, 0·1%). Of these, 49 conditions had an absolute risk of 1·0% or more, while this applied to

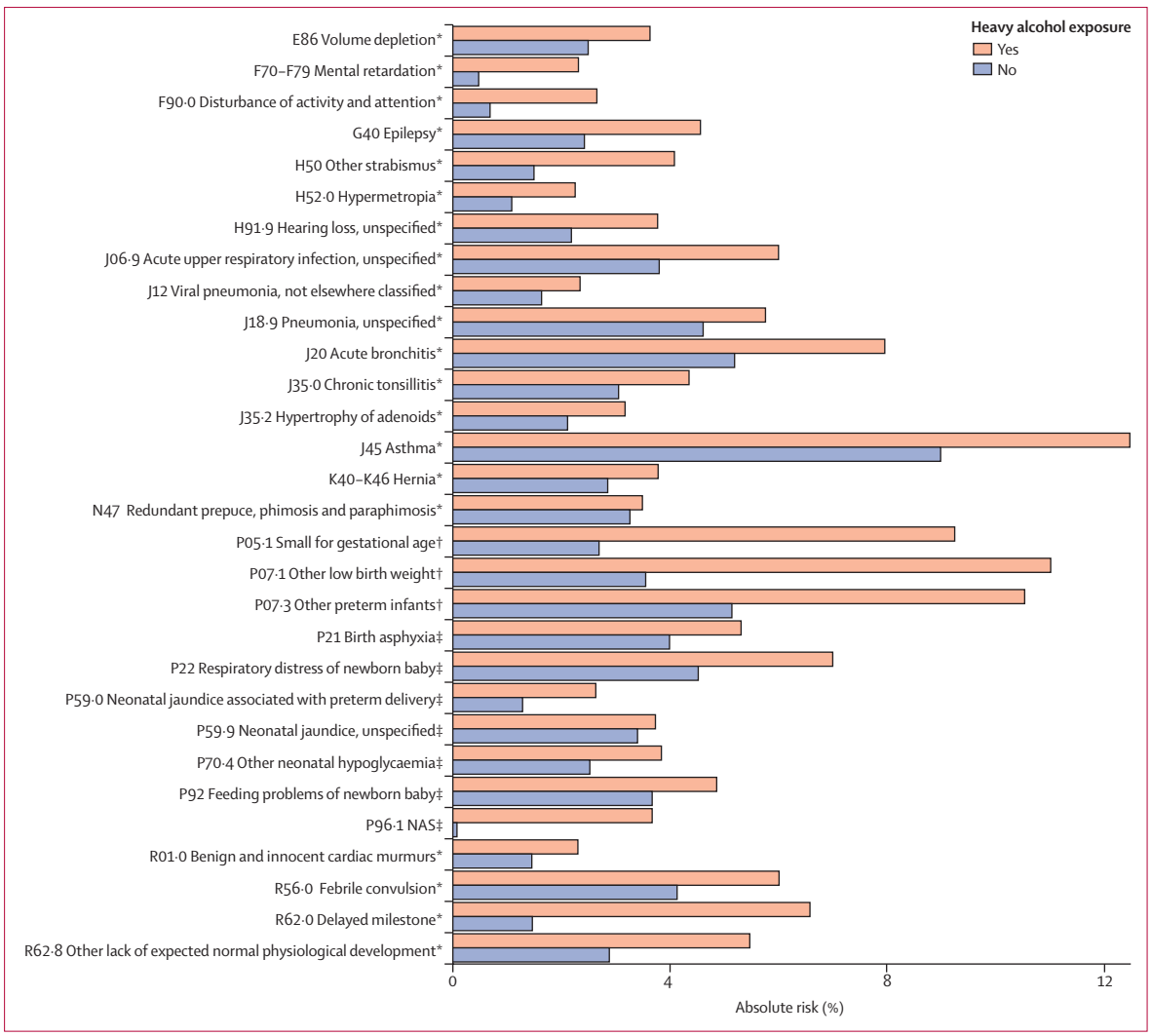

Figure 1: **Pre-identified fetal alcohol spectrum disorder comorbidities with the highest absolute risk in heavy prenatal alcohol-exposed children compared with the reference group**

A complete list of conditions and International Classification of Diseases-10 codes with absolute risks is presented in the appendix (p 15). NAS=neonatal withdrawal symptoms from maternal use of drugs of addiction. *Comorbidities with time onset in childhood or not elsewhere included. †Comorbidities with time onset at birth. ‡Comorbidities originated in the perinatal period.

33 conditions in the reference group. Figure 1 shows the 30 preidentified conditions and figure 2 shows the 30 previously unidentified diseases and health-related problems with the highest absolute risk in heavy prenatal alcohol-exposed children compared with the reference group. The pre-identified conditions were predominantly related to neonatal conditions, brain function, sense organs (vision and hearing), mental and behavioural disorders, and respiratory tract infections. Pre-identified conditions with an absolute risk ratio of 2·5 or more are shown in the appendix (p 3), to highlight rare conditions. These conditions were predominantly brain-related such as microcephaly; delayed development and intellectual disability; behavioural disorders such as Tourette's syndrome; hyperkinetic disorders; intentional self-harm such as use of alcohol; eye and adnexa diseases; neonatal conditions; and birth defects predominantly of the heart, facial appearance, and gastrochisis.

Pre-identified conditions with standardised risk difference of at least 0·5% in heavy prenatal alcohol-exposed children compared with the reference group are presented in figure 3. This referred to 29 conditions (ie, <13% of the 234 conditions), primarily associated with brain function such as seizure disorders, delayed development and intellectual disability, mental and behavioural disorders such as tics and hyperkinetic disorders, ear and respiratory tract infections, and neonatal conditions. The four highest standardised risk differences were found for low birthweight (4·70% [95% CI 3·70–5·71]), small for gestational age (4·63% [3·72–5·55]), delayed milestone (3·81% [2·99–4·64]), and other preterm infants (2·69% [1·71–3·68]; appendix

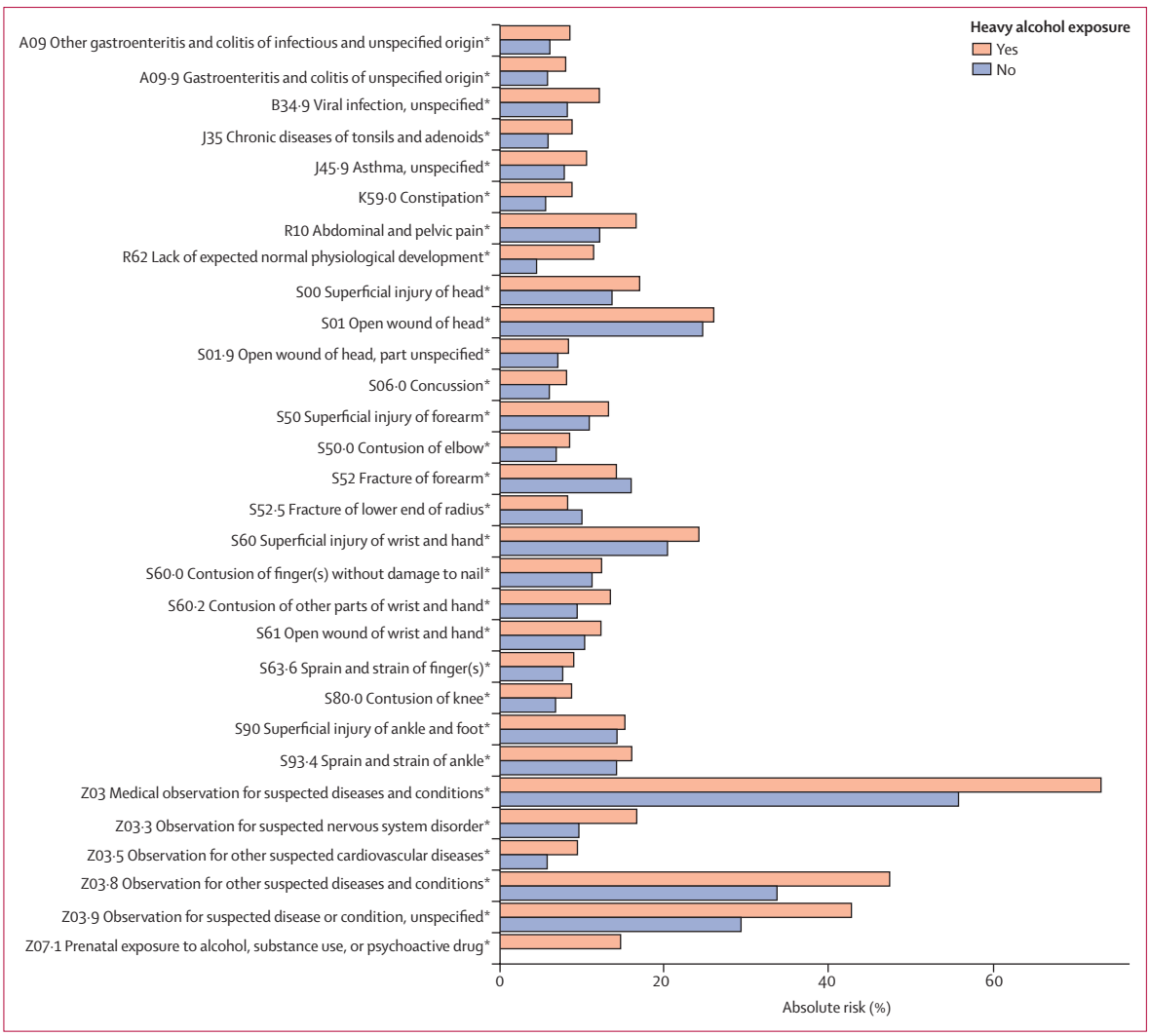

Figure 2: **Previously unidentified diseases and health-related problems with the highest absolute risk in heavy prenatal alcohol-exposed children compared with the reference group**

A complete list of conditions and International Classification of Diseases-10 codes with absolute risk is presented in the appendix (p 49). *Comorbidities with time onset in childhood or not elsewhere included.

pp 45, 48). Results of the sensitivity analyses, presenting conditions with standardised risk differences of at least 0·5% among children either prenatally exposed to acute or chronic alcohol use, compared with the main analyses, are shown in the appendix (pp 7–8). Of conditions with a standardised risk difference of at least 0·5%, we found 18 conditions in children prenatally exposed to acute alcohol use and 43 conditions in children exposed to chronic alcohol use. Notable conditions at risk in the chronic alcohol group were disturbance of activity and attention, tic disorders, strabismus, disorders of refraction and accommodation, anomalies of jaw and tooth position, birth asphyxia, neonatal hypoglycaemia, and neonatal withdrawal symptoms.

In total, we found 719 previously unidentified diseases and health-related problems with an absolute risk of at least 0·1% in heavy prenatal alcohol-exposed children. The absolute risk of previously unidentified diseases and health-related problems, of which 224 conditions had an absolute risk of at least 1·0% in heavy prenatal alcohol-exposed children compared with 174 conditions in the reference group, are presented in the appendix (p 49). Figure 2 shows the 30 conditions with the highest absolute risk among the alcohol-exposed children. The conditions were primarily related to infections; some injuries of head, arm, and hand; and observation for suspected diseases. The 143 (19·9%) of the 719 conditions with an absolute risk ratio of at least 2·5 in the heavy prenatal alcohol-exposed children are presented in the appendix (pp 4–6). These primarily consist of disorders of psychological development, behavioural and emotional disorders; cerebral palsy;

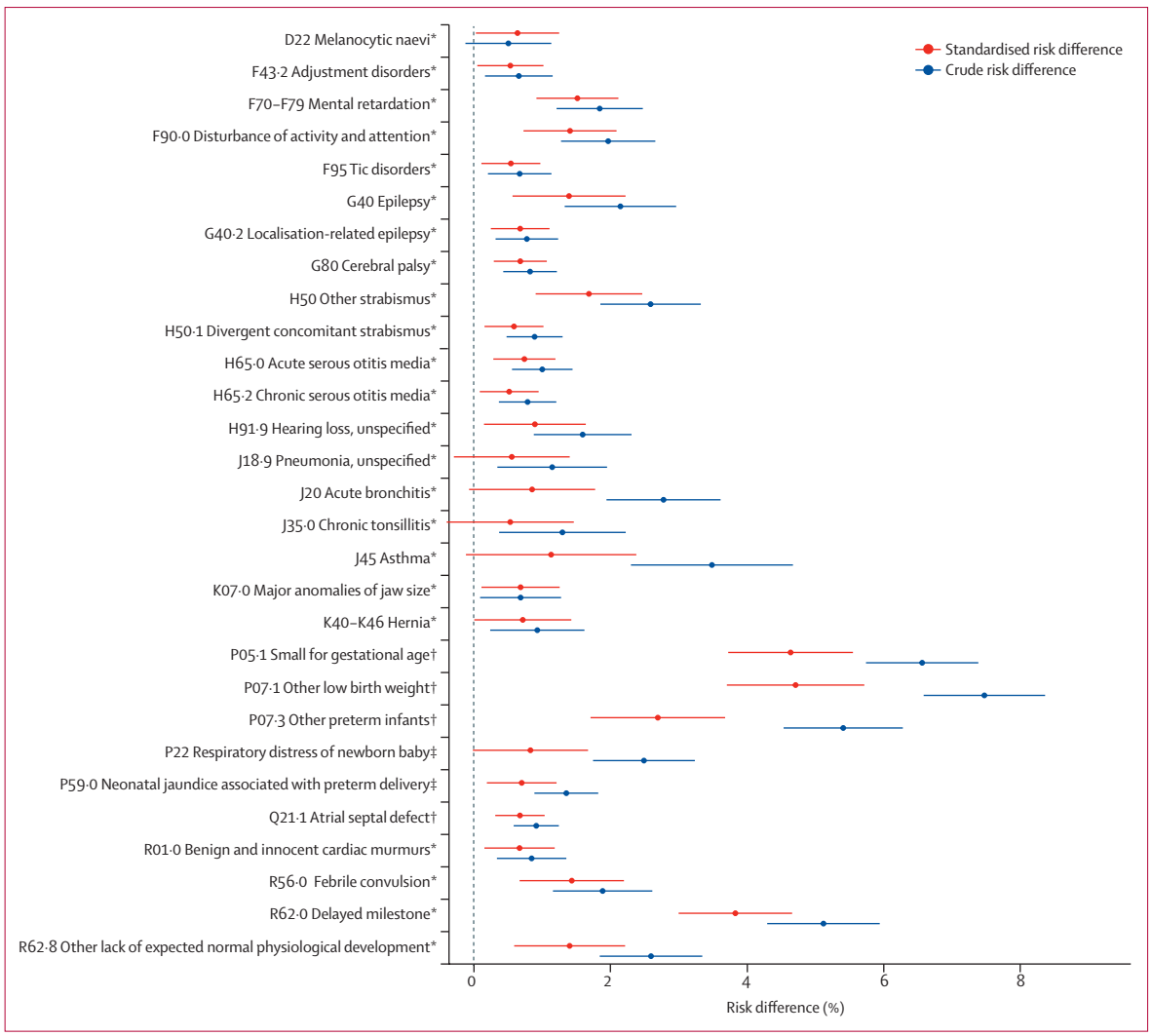

Figure 3: **Pre-identified fetal alcohol spectrum disorder comorbidities with standardised risk differences of at least 0·5% in heavy prenatal alcohol-exposed children compared with the reference group**

Standardised risk differences were standardised to the distribution of the covariates: sex, maternal age, parity, maternal chronic somatic disease and psychiatric disease, prenatal exposure to substance use, and maternal educational level. A complete list of conditions and International Classification of Diseases-10 codes with crude and standardised risk differences is presented in the appendix (p 41). Localisation-related epilepsy refers to localisation-related (focal; partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures. *Comorbidities with time onset in childhood or not elsewhere included. †Comorbidities with time onset at birth. ‡Comorbidities originated in the perinatal period.

visual impairment; infections; prenatal exposure to maternal conditions, medications, and substance use; congenital malformations; injuries; poisoning effects; child maltreatment; and problems related to psychosocial circumstances.

The 32 (4·5%) of 719 conditions with a standardised risk difference of at least 1·0% in heavy prenatal alcohol-exposed children compared with the reference group are presented in figure 4. The 32 conditions were predominantly associated with low birthweight, abdominal pain, body contusion and some injuries, medical observations for suspected diseases, and removal from home. Crude and standardised risk differences for the 719 previously unidentified diseases and health-related problems are summarised in the appendix (p 94). The range of the standardised risk differences was from –1·28% to 10·59%. Results of the sensitivity analyses presenting conditions with a standardised risk difference of at least 1·0% in children prenatally exposed to acute or chronic alcohol use, compared with the main analyses, are presented in the appendix (pp 9–11). The 47 conditions found in children exposed to acute alcohol use were primarily related to infections, headache, abdominal pain, and some injuries of head and upper extremities. The 24 conditions found in children exposed to chronic alcohol use were related to strabismus, hearing loss, low birthweight, delayed development, household dysfunction, and family history of abuse.

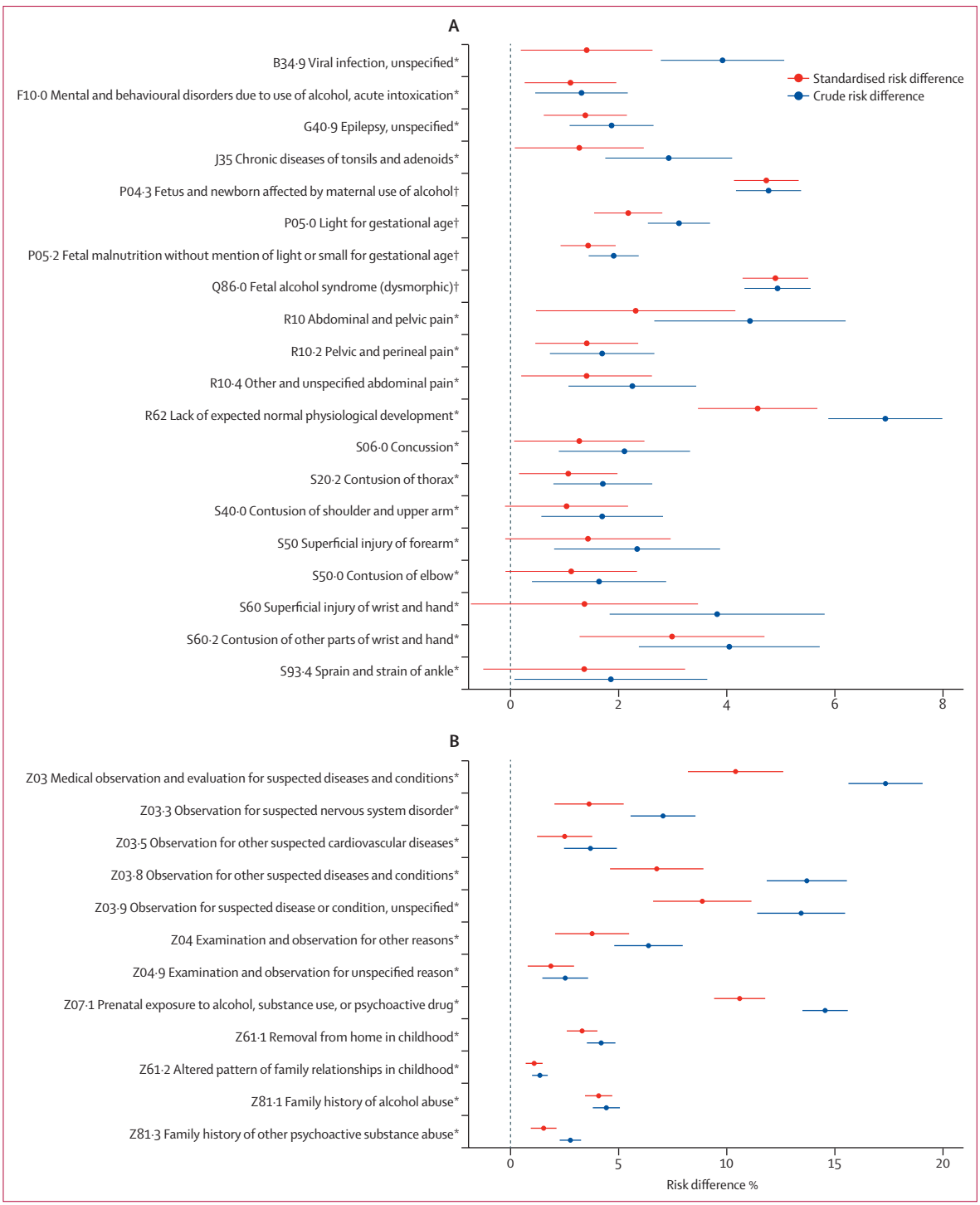

Figure 4: **Previously unidentified diseases and health-related problems within ICD-10 (A and B) with standardised risk differences of at least 1% in heavy prenatal alcohol-exposed children compared with the reference group**

Standardised risk differences were standardised to the distribution of the covariates: sex, maternal age, parity, maternal somatic and psychiatric disease, prenatal exposure to substance use, and maternal educational level at birth. A complete list of conditions and ICD-10 codes with crude and standardised risk differences is presented in the appendix (p 94). ICD-10=International Classification of Diseases-10. *Comorbidities with time onset in childhood or not elsewhere included. †Comorbidities with time onset at birth.

Discussion

Heavy prenatal alcohol exposure is associated with an overall increased risk of child morbidities in Denmark. Of 428 pre-identified prevalent comorbidities in individuals with fetal alcohol spectrum disorder,[4] we found 29 (7%) with a standardised risk difference of at least 0·5%. Furthermore, we found 32 previously unidentified diseases and health-related problems with a standardised risk difference of at least 1·0%.

Conditions with increased risk were primarily associated with brain function such as seizures, delayed development, and intellectual disability; mental and behavioural disorders such as tics and hyperkinetic disorders; ear and respiratory tract infections; and neonatal conditions (such as preterm birth and low birthweight). Heavy prenatal alcohol exposure also leads to increased risk of adverse birth outcomes. Effects on the fetus can play an important role in the pathophysiology of diseases involving several organs. However, our findings show that the brain and neonatal development period seem to be particularly vulnerable to adverse effects from heavy prenatal alcohol exposure.

Overall, our absolute risks were lower than the pooled prevalence estimates reported by Popova and colleagues (eg, our absolute risk for other preterm infants was 10·5% compared with their pooled prevalence of 65·3% in individuals with fetal alcohol syndrome).[4] Furthermore, Popova and colleagues found 18 conditions with a pooled prevalence of at least 50% in individuals with fetal alcohol syndrome, of which five had a standardised risk difference of at least 0·5% in children exposed to chronic alcohol use. The five conditions were related to ear infections, hyperkinetic disorders, visual impairment, and preterm birth. Direct comparison of results might be challenged by methodological differences, as well as national and temporal differences in disease burden.

Prenatal exposure to chronic alcohol use was associated with congenital heart defects, which previous evidence has described with inconsistent results.[23–25] An Australian study with a similar methodological approach also found an association between heavy prenatal alcohol exposure and cerebral palsy.[26]

In our study, prenatal alcohol exposure was associated with a remarkably high increased risk of asthma and respiratory tract infections. Whether alcohol exposure leads to immune-related outcomes or whether the associations are potentially mediated by preterm birth or second-hand smoke remains unknown and further research is warranted.[27]

Among the alcohol-exposed children, 22% were defined as prenatally exposed to substance use. The absolute risk for neonatal withdrawal symptoms was 3·7% with an absolute risk ratio of 50·9. This suggests risk of multiple adverse prenatal exposures. Unfortunately, subdividing substance use according to timing, quantity, or type was not possible. Notably, the standardised risk difference for neonatal withdrawal symptoms is considered to be underestimated, due to equalising correction with the covariate prenatal exposure to substance use.

Conditions with increased risk were mainly associated with abdominal pain, some body injuries, observations for suspected diseases, mental disorders due to alcohol use, and psychosocial problems such as child maltreatment and removal from home. Outcomes at risk are notably heterogeneous in their relation to biology versus environment. Outcomes regarding adverse childhood experiences (eg, household dysfunction) are external factors that perhaps might be more prevalent in families with alcohol abuse, but not necessarily a direct cause of prenatal alcohol exposure. In this context, the crude results for conditions regarding household dysfunction and child maltreatment are particularly concerning. Adverse childhood experiences have been associated with various health conditions and premature death.[28] The increased risk for some injuries to head, thorax, and extremities was notable. It has been estimated that 2–10% of children visiting the emergency department are victims of child abuse.[29] However, our study did not examine this relationship.

The Danish data collection on its citizens enabled this large nationwide cohort study to be done, with inclusion of covariates shown to be associated with overall child morbidities and alcohol drinking during pregnancy. The use of diagnoses and prescriptions to identify individuals with heavy prenatal alcohol exposure is an objective approach that avoids recall bias and potentially identifies individuals who under-report alcohol use during pregnancy.

We consider the exposed to be individuals who experience the most critical health consequences of alcohol. However, the data holds no information on timing, quantity, frequency, or type of alcohol consumed. Some women classified as heavy drinkers might have abstained from alcohol (eg, of 635 women with pre-pregnancy alcohol treatment 77 women received treatment within 1 year post partum). Furthermore, a prenatal alcohol-attributable diagnosis in a child does not by definition indicate heavy alcohol exposure. By contrast, not all heavy drinkers have an alcohol-related hospital contact. Taking the large reference group into account, this misclassification bias will probably underestimate our results. Nonetheless, our findings of conditions at risk correspond to several diagnostic categories delineating fetal alcohol spectrum disorder,[2] supporting a high specificity of our methodological approach.

Our study design provided a comprehensive list of outcomes with estimates, allowing a unique insight into the magnitude and patterns of conditions in heavy prenatal alcohol-exposed children. However, our diagnoses were limited to hospitals, not including conditions diagnosed by the general practitioner, which possibly underestimated the absolute risk of less severe conditions. By contrast, detection bias in children with fetal alcohol

spectrum disorder might have influenced results in the opposite direction, although 21·2% of exposed children had a prenatal alcohol-attributable diagnosis, of which 5·1% had fetal alcohol syndrome. Data registration was for administrative purposes rather than science. Due to the observational design, unmeasured confounding factors might have affected our results.

Another limitation is the age span of our study population (eg, several psychiatric conditions such as affective disorders and schizophrenia, which most commonly present from late adolescence, were absent or with a low occurrence). Our study mapped risks of all frequently recorded conditions, and risks might—for previously unidentified diseases and health-related problems—be of a more hypothesis-generating nature. Future studies should examine school performance and function because many higher cognitive, behavioural, and social problems appearing at school might not be captured in the diagnoses included in our study.

Our study emphasises the complexity of heavy prenatal alcohol exposure in children with a hospital contact by identifying a wide range of diseases and health-related problems such as adverse childhood experiences. These cumulative risks place the child in an extremely vulnerable position, despite the Danish welfare system (social welfare, free health care, and free education). Alcohol consumption during pregnancy is common and a stronger preventive effort is needed to advance health. Regarding harm prevention, resilient pre-conceptional health care can make a difference by promoting healthy behaviours, starting in the transition from adolescence to adulthood. To accelerate gains for children with fetal alcohol spectrum disorder, we suggest an increase in awareness and attention to child and adolescent health risks. This can be achieved by recalibrating interventions towards an organised multi-professional cross-sectoral integrated and family-oriented approach. Health-promoting care and support is a multifaceted complex task including physical, mental, and social parts with inclusion and care for the entire family.

In conclusion, heavy prenatal alcohol-exposed children face potential challenges to healthy physical, psychological, and social development due to prenatal and postnatal environmental issues. This group of children, and their families, are highly vulnerable and carry a notable burden of disease.

Contributors

MB, CT-P, TAG, KS-L, USK, and BMH conceptualised and designed the study. MB, CT-P, TAG, and AM directly accessed and verified the underlying data reported in the manuscript. MB, CT-P, TAG, and AM did the statistical analysis. KKS and MB created the figures. MB, USK, and BMH wrote the first draft of the manuscript. All authors interpreted the results, critically revised the manuscript for important intellectual content, and gave final approval for the version to be published. TL, CT-P, and MB were responsible for project administrative and material support. USK, CT-P, BMH, KS-L, and TAG supervised the study. All authors had full access to all the data in the study and take responsibility for the decision to submit for publication.

Declaration of interests

CT-P reports grants for studies from Bayer and Novo Nordisk unrelated to the current study. All other authors declare no competing interests.

Data sharing

The nationwide data contains personally identifiable and sensitive information which, according to the Danish Data Protection Agency and the General Data Protection Regulation, can only be accessible within the protected environment of Statistics Denmark or similar environments. Others with interest in the data need to collaborate with the authors or with other groups authorised to work in these protected environments. No additional related documents will be available.

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