Fetal Alcohol Spectrum Disorders

Maastricht University

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Knowledge Synthesis

Fetal Alcohol Spectrum Disorders

S. Roozen, G. Kok, L.M.G. Curfs

A report commissioned by ZonMw

ZonMw

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Sylvia Roozen, Gerjo Kok and Leopold Curfs

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Preface

This report describes current knowledge and gaps in knowledge regarding FASD in the Netherlands. The steps of Intervention Mapping (IM) are used as a framework for analyzing this situation. The first chapter provides a brief introduction to the methodology used in IM, and is followed by an overview of questions and issues related to FASD, as formulated by the Dutch Organization of Health Research and Development (ZonMw). The second chapter focuses on primary prevention, and explores causes of and risk factors related to FASD. The third chapter addresses secondary and tertiary prevention, including screening, early detection, and intervention techniques. Issues regarding management and care for people with a diagnosis on the FASD spectrum are described from the perspective of enhancing quality of life by reducing the impact caused by FASD. The fourth chapter summarizes state of the art FASD knowledge and challenges. Conclusions and recommendations, together with a prioritization of FASD-related knowledge needs and questions, are presented in the fifth chapter.

Maastricht: Sylvia Roozen, Gerjo Kok and Leopold Curfs

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Chapter 1
Introduction

1. INTRODUCTION

Fetal alcohol spectrum disorders (FASD) can result in serious health problems affecting communities worldwide. FASD is an umbrella term used to describe a range of birth defects caused by prenatal exposure to ethyl alcohol. Alcohol may result in mild to severe damage to the development of an unborn baby [1–6]. This damage can lead to lifelong physical, behavioral, and cognitive disabilities. Depending on the nature and severity of the damage, the following diagnoses under the FASD umbrella term can be given: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol-related neurodevelopmental deficiencies (ARND), alcohol-related birth defects (ARBD), or neurobehavioral disorder-prenatal alcohol exposed (ND-PAE) [1,7–11]. FASD is a disorder that is 100% percent preventable, as alcohol consumption during pregnancy can be avoided. FASD is therefore one of the most important preventable forms of non-genetic birth defects associated with intellectual disability [12–15].

This FASD knowledge synthesis provides an overview of current knowledge and gaps in knowledge regarding FASD prevalence, prevention, diagnosis, management, and treatment. It also provides a needs assessment with regard to FASD which focuses on health care and prevention. The synthesis ends with recommendations for an action plan based on a prioritization of FASD knowledge needs and questions. The framework and methodology outlined in this report are grounded in the Intervention Mapping approach.

Intervention Mapping (IM) is a protocol that is used for planning theory- and evidence-based health promotion programs based on the best current theory and evidence [16,17]. The purpose of IM is to provide those planning health promotion programs with a framework for effective decision making at each step in the process of intervention development, implementation, and evaluation. IM is a planning approach that is based on using both theory and evidence as foundations for decision making. It takes an ecological approach to assessing and intervening in health problems and engendering community participation. IM was developed in reaction to a lack of available comprehensive frameworks for health promotion program development. It was designed to guide health promoters in developing the best possible intervention. The key words in this protocol are planning, research, and theory. More specifically, IM ensures that theoretical models and empirical evidence guide planners in two areas: (1) the identification of determinants related to behavioral and environmental causes of a target problem, and (2) the selection of appropriate theoretical methods and practical applications that can be used to address these identified determinants.

IM provides a vocabulary for needs assessment, program planning, procedures related to planning activities, and technical assistance by identifying theory-based determinants and matching them with appropriate methods for change. The IM protocol de-

scribes the iterative path from problem identification to problem-solving or mitigation. Each of the six steps of IM comprises several tasks, each of which integrates theory and evidence. The completion of the tasks within a step creates a product that is the guide for the subsequent step. The completion of all of the steps serves as a blueprint for the design, implementation, and evaluation of an intervention based on a foundation of theoretical, empirical, and practical information. The six steps (and related tasks) of the IM process are as follows. Step 1 is the development of a logic model of the problem, and involves conducting a needs assessment or problem analysis by identifying what, if anything, needs to be changed, and for whom. Step 2 involves setting program outcomes and objectives for each stage of the logic model of change. This entails creating matrices of change objectives by combining (sub-)behaviors with behavioral determinants in order to identify which beliefs should be targeted by the intervention. Step 3 is program design, that is, selecting theory-based intervention methods that match the determinants into which the identified beliefs aggregate, and translating these into practical applications that satisfy the parameters for effectiveness of the selected methods. Step 4 focuses on program production, that is, integrating the practical applications into an organized program. Step 5 involves developing a program implementation plan for the adoption, implementation, and sustainability of the program in real-life contexts. This entails identifying program users and supporters and determining what their needs are, and how these needs can be met. Step 6 involves the production of an evaluation plan so that effect and process evaluations can be carried out to measure program effectiveness.

IM is a helpful tool that can be used to design health promoting programs in a systematic and evidence-based manner in order to increase the chance of success in reducing prenatal alcohol exposure and FASD [18]. It is true that it is a complex and time-consuming process, reflecting the difficulty of changing health behaviors. IM has helped to bring the development of interventions to a higher level, indicating that the advantages associated with this approach outweigh any disadvantages.

This knowledge synthesis will primarily focus on Step 1 of IM - the needs assessment or problem analysis undertaken to identify what needs to be changed and for whom. Where possible, attention will also be given to the next steps of IM. The following important knowledge issues, as formulated by the Dutch Organization of Health Research and Development (ZonMw), will be addressed:

- Description of current knowledge and gaps in knowledge about FASD *(Chapters 2 and 3)*
- Identification of shortfalls in the Dutch health care system related to FASD *(recommendations provided throughout chapters)*
- Inventory of existing databases in the Netherlands relevant for FASD *(paragraphs 2.3, 2.6, 3.5)*

- Identification of relevant stakeholders in the Netherlands as related to FASD *(in particular paragraph 2.10)*
- Identification of problems related to FASD in terms of stigmatization and stereotyping *(paragraph 2.11)*
- Ethical and legal issues related to FASD *(paragraph 2.12)*
- Identification of evidence-based prevention strategies designed to reduce the alcohol consumption of pregnant women and women of a childbearing age *(paragraph 2.13)*
- Description of FASD diagnostic practices *(paragraph 3.2)*
- Description of costs and benefits analyses related to FASD care and treatment interventions in the Netherlands *(paragraph 3.6)*
- Identification of effective or promising interventions / treatment methods for FASD *(paragraph 3.7)*

Figure 1 schematically represents the most important concepts that will appear in this report. The top half concerns primary prevention: no alcohol exposure (Chapter 2), while the bottom half concerns secondary and tertiary prevention: early diagnoses, optimal management and care (Chapter 3). In addition to the mother and child, other relevant individuals (actors) are depicted. The relevant sub-disciplines involved in the various steps are successively described in this report. Stigma as well as legal and ethical issues relate are discussed in relation to each step. The report suggests different theory- and evidence-based interventions that could be implemented in relation to various target groups.

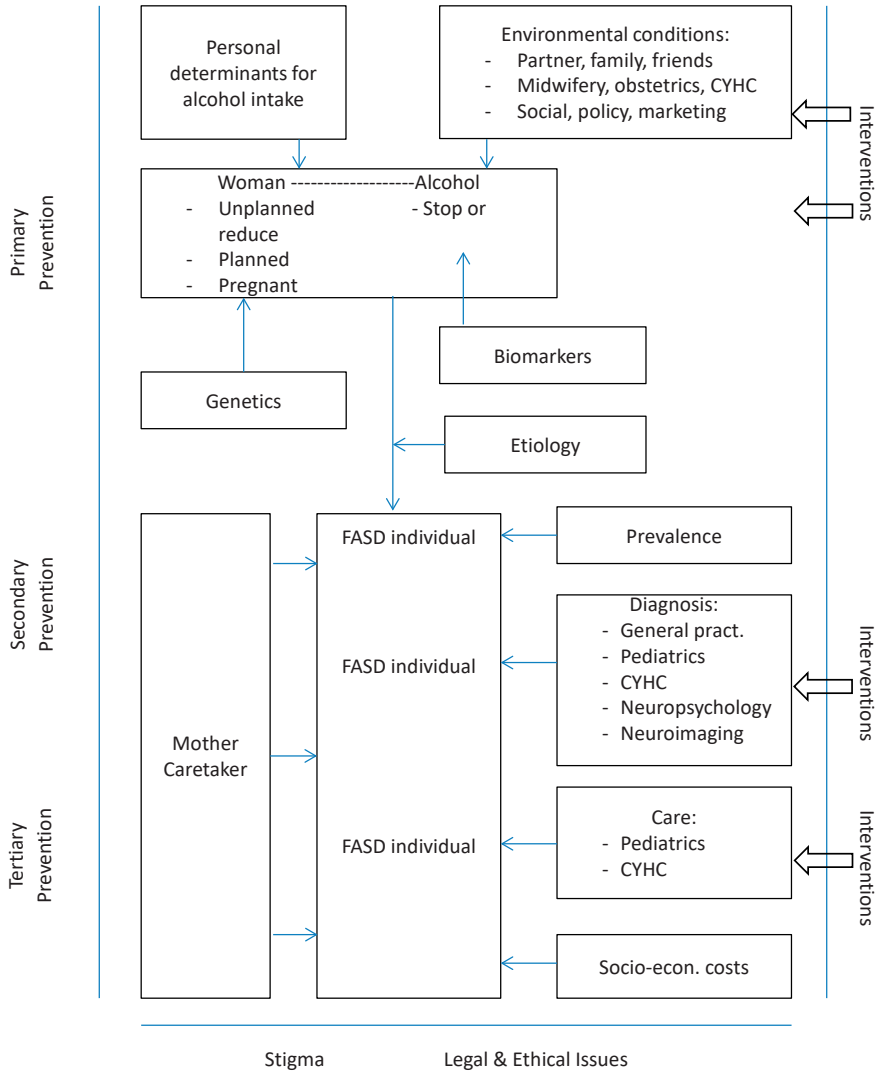

Figure 1 Overview of Chapter and Topics Discussed in This Report

Figure 1 Overview of Chapter and Topics Discussed in This Report

Chapter 2
Primary Prevention

2. PRIMARY PREVENTION

"Many disabilities have an unknown etiology or cause, but FASD is associated with prenatal alcohol exposure which may cause lifelong physical, behavioral, and cognitive disabilities. It is 100 per cent preventable" (Carpenter, Blackburn, and Egerton, 2013 p.13; [19]).

2.1. Introduction

Different levels of functioning may be affected in persons diagnosed within the spectrum of FASD, including abstract reasoning, information processing, attention, executive functioning, visual perception, social cognition and interaction, memory, and self-regulation. This can result in difficulties with daily living skills (e.g., money management), living independently, and academic achievements (e.g., school failure), as well as increasing the likelihood of getting into trouble with the law [12,20–23].

Prenatal alcohol exposure not only reduces the quality of life of affected individuals, but also that of their families and those around them. There are many stakeholders with regard to FASD, including parents (biological and adoptive parents), persons affected by FASD, government (various departments), health care professionals, social workers, teachers, researchers, and policy makers [18]. FASD carries a social and economic burden in every society where women drink during pregnancy. There is a clear need for both prevention and intervention [15,18,24].

The goal of primary prevention is to prevent prenatal alcohol-exposed pregnancies. After a brief historical outline of alcohol consumption, the following paragraphs will discuss current knowledge and gaps in knowledge, and provide recommendations related to FASD etiology and pathogenesis, biomarkers for alcohol use, genetic factors and alcohol consumption, the role of maternity care, FASD prevalence, risk behaviors and target groups, psycho-social determinants of drinking behavior, environmental conditions, stigma, legal and ethical issues, and interventions that can be used to prevent harm caused by alcohol exposure in pregnancy.

2.2. Alcohol Consumption

Two scenes from the BBC series 'Inspector Linley Mysteries' show the main character's wife opening a champagne bottle to celebrate her pregnancy - one when she announces her pregnancy to the father, the other when she tells a female colleague [25]. Only one of her remarks shows some sensitivity to the issue, when she says she is allowed to have at least one drink. The scene is clearly not intended as a statement by the series' authors regarding the woman as an irresponsible person (she loses the fetus later on in the series due to an accident), but it indicates that in 2004, pregnant

women drinking alcohol was not a taboo, nor was it considered wholly inappropriate, as it is today.

In the 19th century, in protestant cultures, women drinking alcohol - not only those who were pregnant - were condemned, mainly on moral grounds. Little concrete medical knowledge was available on the teratogenic effects of alcohol use, but alcohol use in general was seen as undermining one's health. Many iconographic images appear to depict the despicable nature and detrimental effects of women drinking alcohol. The consumption of spirits was chiefly a male affair, and also a public one. The temperance movement, and later teetotalism, directed their efforts mainly towards men. Women were considered to be custodians of ethical standards. They and their children were seen as victims of men's drinking rather than depicted as the source of harm to the child and family. Additionally, social Darwinists considered alcohol use as a source of hereditary degeneration, with alcohol damaging reproductive cells, in both men and in women [26]. In fact, due to dwindling consumption rates and American Prohibition, the topic of alcohol and reproductive health became a non-issue in research as it was not considered a priority in terms of public reproductive health [26].

Together with a declining overall consumption in the early 20th century, women's drinking practices were changing, especially during U.S. prohibition. In the USA, the "roaring 20s" saw the birth of the flapper - and of cocktail hour, during which men and women could drink together in bars (or speakeasies) and restaurants, an unlikely scene in earlier days. After the Second World War, alcohol consumption increased in many Western countries, with most consumption taking place in private settings, and with men and women drinking together. For example, in the Netherlands, per capita consumption quadrupled after the war, and was as high in 1980 as at the end of the 19th century. In general, female consumption was half that of men, with abstention (not-drinking for specific time periods) also higher among women [27].

This rise in consumption has rekindled public health concerns. In the 1970s, WHO initiatives formulated the so-called single distribution model, highlighting the harm caused by alcohol consumption. Basically, in this public health model, overall exposure to alcohol is the main target for prevention, and general temperance is the most important policy aim. Price and tax measures and reduced availability were thought to be instrumental in reducing overall exposure [28]. Implementation of these measures in the Netherlands has not been very successful, and alcohol policies are often targeted at subpopulations which are considered to be the most vulnerable, such as the underage youngsters and pregnant women.

The first mention of FAS appeared in studies conducted by Lemoine et al. in 1968 [29] and Jones and Smith in 1973 [30], but the topic only received attention as a major public health problem in the late 1980s and early 90s, when the issue acquired elements of a 'moral panic', with exaggerated claims of harm [31]. In this period, the

notion of pregnant women drinking alcohol was increasingly met with public and moral condemnation. Rhetorically, the phenomenon was presented as being part of an iceberg, with vast numbers of under-diagnosed cases of FAS children. Scientific reports on newly discovered effects led the media to pick up stories that contributed to the public image of female drinking as a major threat to children. However, scientific proof failed to back up this idea of a large number of unrecognized cases, and the rhetorical fervor subdued. What remains undisputed is the harm that excessive drinking during pregnancy can cause in the off-spring of mothers who drink, but the message in both scientific publications and popular media has become more nuanced. However, pregnancy is still featured on the mandatory warning labels introduced in the US in 1988. While there is no mandatory labelling in effect in the EU, some EU countries do have national regulations, for example, mandating a pregnancy warning on alcoholic beverage containers (i.e. France).

Social and policy responses towards the issue of heavy drinking during pregnancy seem to differ between countries, with some states and countries taking punitive measures, and others implementing more supportive laws and measures. Drabble et. al. (2011) [32] noted that fear of stigmatization, and the consequent creation of a threshold to care and intervention, is a reason to implement more supportive measures. Discussion on whether to caution all pregnant women to refrain from any alcohol intake remains an issue for debate in many countries. Although evidence is not unequivocal, most countries have decided 'rationally' to err on the side of caution in suggesting total abstinence, while others have provided conditional advice [33].

In the Netherlands, increasing attention has been given to children born to pregnant women who are addicted to substances or use them excessively [34], and suggestions have been put forward to adapt the rules concerning coercive treatment and the fetal age at which legal intervention is possible [35,36]. There has also been a noticeable shift in public health policy in the Netherlands. The conclusion of a study among women in the province of Drenthe in 1987 was that a specific public health campaign aimed at pregnant women would not be effective due to low consumption in the target group [37]. The recent advice provided by the Dutch Health Council - which promotes abstention - is indicative of a change in the conception of prenatal risks, although, as in 1987, one third of pregnant women still consumes alcohol, albeit in limited quantities. The Dutch Health Council reported that 80% of women of childbearing age indicated that they use alcohol (2005) [38]. In the Netherlands, the department of TNO child health (Lanting et al., 2015), among other organizations, have published data about alcohol consumption during pregnancy (see also paragraph 2.7: risk behaviors) [39,40]. Within the current ZonMw program 'Zwangerschap en Geboorte' (Pregnancy and Birth) [41], some of the projects collect new data on alcohol consumption among pregnant women (see also paragraph 2.5: maternity care). Figure 2 presents an overview of current alcohol consumption estimates (worldwide, Europe, and the Netherlands) among (pregnant) women.

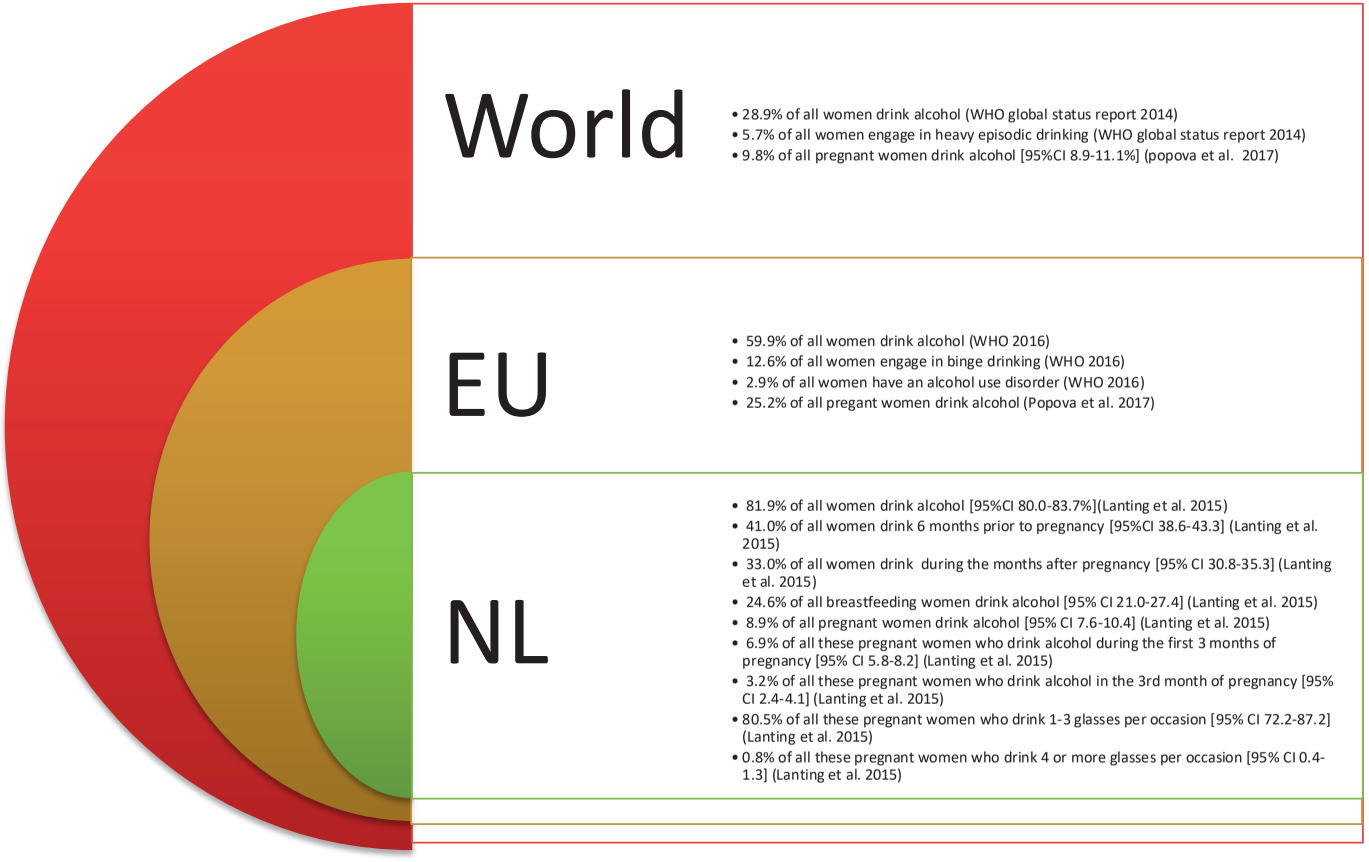

Figure 2 Alcohol Consumption Estimates Among (Pregnant) Women Worldwide (WHO Global Status Report 2014, Popova and Colleagues 2017) [5,42], Europe (WHO 2016, Popova and Colleagues 2017) [42,43] and the Netherlands (Lanting and Colleagues 2015) [39]

2.3. Etiology and Pathogenesis

Current knowledge regarding molecular pathways

The mechanism of the teratogenic effects of prenatal alcohol exposure is not well understood yet. This section describes the current pathophysiological understanding of Fetal Alcohol Spectrum Disorders (FASD) and possible pathways for treatment.

Alcohol (specifically ethanol, EtOH) is metabolized in two major ways [44]: by ADH (alcohol dehydrogenase) and by the CYP2E1 (cytochrome P450 2E1) pathway. ADH is a cellular enzyme which is responsible for about 90% of EtOH clearance. CYP2E1 is located in the liver and brain and is responsible for about 10% of clearance, unless the EtOH concentration rises. ADH (KM = 4.5 mg/dl) is saturated much earlier than CYP2E1 (KM = 74 mg/dl). In the human fetus, CYP2E1 is active from week 16, while ADH is only active from week 26; both have much lower enzyme levels and activity than in adults [45]. Due to accumulation and lower clearance in the fetus (or embryo), alcohol concentrations are higher and longer lasting in the fetal environment.

EtOH and its catabolite acetaldehyde are toxic themselves, but the major damage pathway is increasing oxidative stress. ADH and CYP2E1 (and to a much lower degree catalase [CAT]) catalyze the same reaction from EtOH to acetaldehyde, but CYP2E1 produces radical oxygen species (ROS) as side products. In an uncontrolled manner, ROS oxidize lipids, proteins, and other metabolites, and cause DNA damage (DNA damage response pathway). Increased DNA damage triggers apoptosis pathways leading to neurodegeneration. Serotonergic neurons seem to be especially susceptible to EtOH-induced apoptosis [45]. EtOH causes dysregulation of mitochondrial bioenergetics in neuronal cells leading to inhibition of mitochondrial proliferation and differentiation, reduction of mitochondrial volume, and a decrease in activity of respiratory chain complexes and ATP synthase, leading to a general generation of ATP reduction, and depletion of mitochondrial GSH (reduced glutathione). Furthermore, EtOH itself as well as oxidative stress-induced downstream pathways causes changes in DNA methylation (mechanism of EtOH inhibiting TET proteins) leading to changes in epigenetic imprinting which may cause changes in brain structure and function. Initial studies indicate that these methylation changes are also found in the germ cells (and offspring) of EtOH-exposed males [46].

The cellular pathways involved in clearing ROS (which also arise in the respiratory chain and several other normal parts of the metabolism) involve a battery of enzymatic and non-enzymatic pathways including SOD, CAT, GPX, (reduced) glutathione, and several antioxidant metabolites (e.g. tocopherol, melatonin). Application of antioxidants has been shown to rescue some EtOH toxicity-induced phenotypes *in vitro* but, to date, the *in vivo* application trials have not been as successful, possibly due to the bioavailability at the point of need (see treatment).

The developing brain is especially in danger of damage due to elevated ROS levels. First, it has the highest oxygen metabolic rate of all body tissues. Second, it is rich in unsaturated fatty acids and autoxidable neurotransmitters which are substrates for ROS [47]. Third, the reaction with ROS generates superoxide, quinones and semiquinones, which are again highly reactive radicals. Fourth, the levels of antioxidant enzymes are lower in the brain than in other tissues (SOD, CAT, GPx). Finally, fetal cells are more in danger than adult ones because of a lower level of enzymes in general.

The downstream effects of increased oxidative stress are different depending on individual exposure and disposition (Figure 3). A decrease in cell proliferation and cell survival (due to increased apoptosis) has been observed, as well as effects on homeostasis in general (e.g. via the FOXO pathway [48]), effects on neurogenesis and neuronal migration, dysregulation of gliogenesis, alterations in gene expression and DNA methylation leading to changed levels of growth factors, cell adhesion molecules and neurotransmitter system. These are mainly pathways which coordinate growth, structure and function of the central nervous system, but other organs (for example the heart or immune system) can also be impaired (Figure 4).

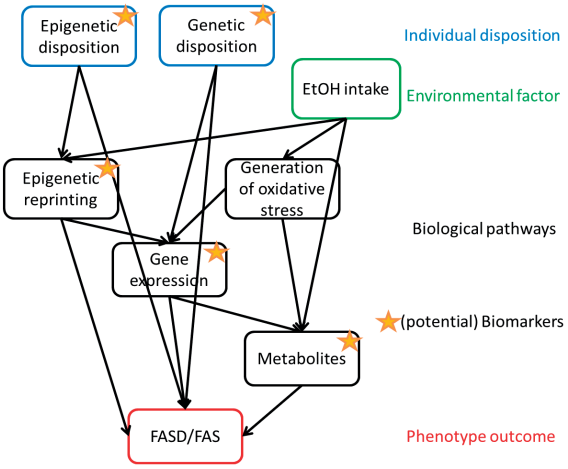

Figure 3 Factors Influencing FASD Outcomes. Individual Disposition and Environmental Factors Trigger the Biomolecular Mechanisms That Lead to Disease Development. Biomarkers Are Possible in Any or the Molecular Data Domains

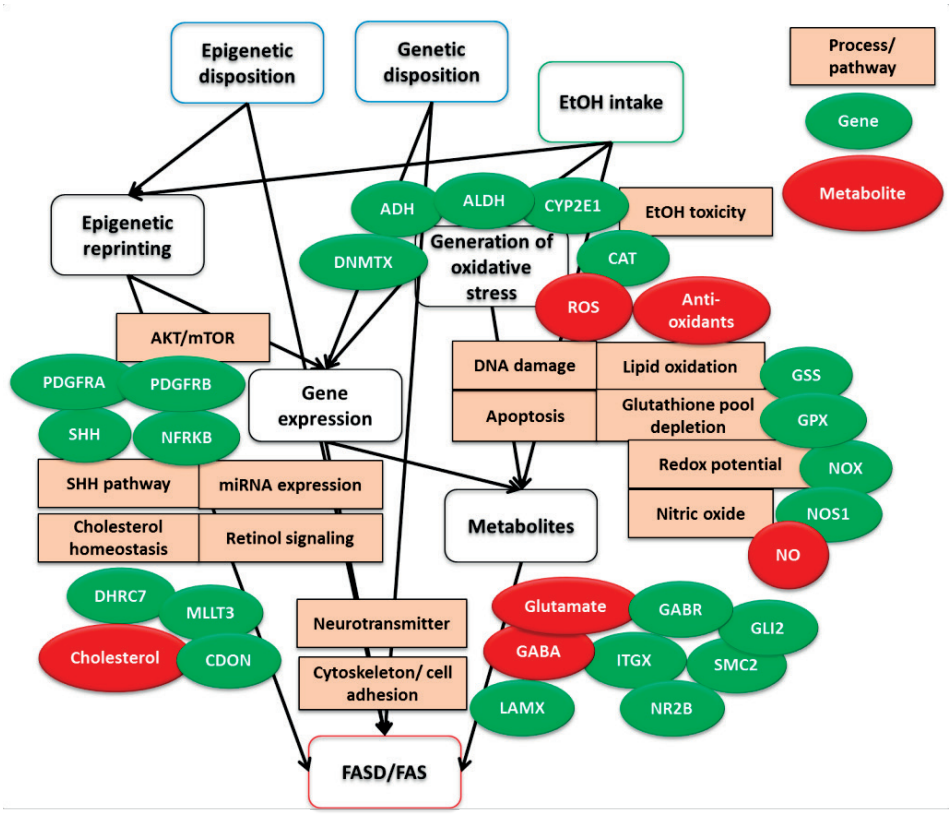

Figure 4 Known Biological Processes/Molecular Pathways, Genes and Metabolites in EtOH Downstream Effects Leading to Adverse Developmental Outcomes Known as FASD

Treatment

As oxidative stress is the major pathway involved in EtOH toxicity in FASD, antioxidants would be the logical treatment of choice. There have been several studies demonstrating the successful rescue of EtOH-induced damaged phenotypes *in vitro* and *in vivo* animal models using Vitamins C and E, folic acid, glutamine, boric acid, choline, and selenium. Unfortunately, such treatments have shown no significant effects when used in humans [45]. Generally, the use of antioxidants to treat oxidative stress-related diseases is highly questionable, as the most reliable reviews indicate a lack of effect (e.g., in relation to gastro-intestinal cancer [49], age-related cataracts [50], or liver diseases [51]).

As EtOH is known to interfere with several biological pathways, e.g. the cholesterol-SHH pathway, experiments have been carried out in zebrafish, demonstrating that supplementation with cholesterol can rescue the phenotype [52] (Figure 4). DHM, a GABA receptor antagonist, has been shown to neutralize EtOH effects on GABA recep-

tor pathways and has some protective effects in rats [45]. Neuroprotective peptides and neurotrophic growth factors have also been also investigated *in vitro* with some success [45].

Chokroborty-Hoque et al. [53] have stated that brain development goes on after birth (and ends at adolescence), so there is time and possibility for improvement. These researchers have proposed that antipsychotic drugs (which include antidepressants or stimulants) could be used to treat intellectual disabilities including psychosis via changes in DNA methylation (and post-natal enrichment) associated with FASD.

Knowledge gaps

In short, the main gaps in knowledge in relation to FASD include that there is no clear pathophysiological understanding of these disorders, no cure, no safe dose for EtOH intake during pregnancy, and, as yet, no reliable biomarker for FASD detection and estimation of susceptibility (Figure 3). Currently, research on FASD includes too many factors that overlap and confound the results to allow any clear conclusions to be drawn. These factors include the following:

- EtOH intake: amount and timing, drinking behavior (binge or events)
- Genetic predisposition: alleles of ADH, CYP2E1 etc.
- Epigenetic predisposition and modifications
- Maternal body profile: age, weight
- Nutrition and lifestyle: amount of antioxidants, fatty acids, iron, exercise
- Drugs: medication
- Comorbidities which involve oxidative stress: cardiovascular diseases, atherosclerosis, cancer, diabetes, neurodegenerative diseases including Parkinson's disease and Alzheimer's disease, toxicity of heavy metals, radiation injury, vitamin deficiency, inflammation (bacterial or viral infection, autoinflammatory processes) [54].

In terms of elucidating the pathology, biomarkers and treatment options associated with FASD, the lack of clinical evidence available points to the need for further research. Animal studies give valuable insight into the mechanisms but are not fully translatable to humans.

Recommendations

We recommend that continuing research should be devoted to five key areas. Below, each area is briefly described. Any gaps in current knowledge and opportunities for more research are highlighted.

1. Genomic data - genetic variation creates different susceptibility for FASD. The genetic background of FASD susceptibility is not yet fully understood but there are hints that different varieties of ADH, CYP and taste receptors play a role. For example, GWAS studies have not yet been carried out on FASD.

2. Epigenetic data - There is some evidence that (1) epigenetic processes are involved in disorder development and progression, as ethanol influences DNA methylation processes and (2) epigenetic changes due to ethanol influences in parents play a role in embryonic development and might be inherited in the following generation. However, the mechanisms underlying these effects are not yet fully understood. There are drugs available which influence DNA methylation events - do they have potential to restore FASD imprinting?

3. Gene expression data - transcriptomics and proteomics change as direct downstream effects of ethanol. There have been initial reports mentioning that gene expression profiles are significantly changed, and one meta-study has even indicated systemic downregulation of gene expression. Yet there are still several unanswered questions: is this general downregulation of gene expression reversible? Can it be influenced by drugs? Which gene expression profiles could be used as biomarkers, in particular to detect the effects of low and medium EtOH intake? And what further insight into the mechanisms of EtOH induced pathology can be obtained from gene expression profiles?

4. Metabolomics data – Areas of interest include: (1) metabolites of ethanol metabolism and (2) metabolites of ethanol-induced pathology. Due to their easy availability in body fluids, meconium or hair, analyzing metabolites may be a highly interesting way of yielding biomarkers not only for EtOH consumption behavior but also for early FASD detection. As single metabolites tend to fail in the detection of low/medium EtOH intake, especially long after after EtOH intake, multi-metabolite (or metabolomics) profiles could provide higher sensitivity and specificity. Another open question concerning EtOH metabolism is whether there are reactive nitrogen species involved in the generation of oxidative stress. Furthermore, it is unknown whether any of these biomarkers could be used for diagnosis. And if so, for whom, and when?

5. Linked Data - Linked data and especially FAIR data (Findable, Accessible, Interoperable, Reusable) [55] is especially useful for fields of research where little primary data is available, as in the case of rare disorders. Collecting and combining data from different sources, and then re-analyzing these can all add value to data provided by smaller individual studies [56]. For FASD-related data, there is currently no public database, but there are several local (clinical) databases which could provide a starting point.

2.4. Biomarkers For Alcohol Use

Current knowledge

Bearer and colleagues (2004) [57] among others, have discussed different biological samples in which biomarkers indicating prenatal alcohol exposures can be measured. These include maternal samples (urine, hair, blood, breath, saliva, gasses acquired through a skin patch, breast milk), fetal samples (blood, chorionic villus, amniotic fluid), and newborn samples (cord blood, placenta, umbilical cord, amniotic fluid, urine, hair, breath, saliva, vermix, gasses acquired through a skin patch, meconium). Advantages and disadvantages of each of the biomarkers are discussed.

Chabenne and colleagues (2014) [58] divide FAS biomarkers into eight major types: (1) clinical biomarkers; (2) molecular biomarkers; (3) omic biomarkers; (4) imaging biomarkers; (5) meconium biomarkers; (6) cord blood biomarkers; (7) anatomical biomarkers; and (8) neurobehavioral biomarkers.

In the Netherlands, Wassenaar and colleagues (2016) [59] point out the importance of using relevant biomarkers to detect alcohol consumption during pregnancy.

The assessment of alcohol abstinence and alcohol use in pregnant women remains a major diagnostic challenge. On the whole, health care workers have to rely on the information provided by the mother and family and on psychometric tests. However, these methods might be unreliable due to the social stigma associated with alcohol use in pregnancy, leading to substantial maternal under-reporting. Therefore, sensitive and specific biomarkers of alcohol use could help to identify women at risk of having a child with fetal alcohol spectrum disorder (FASD). This would allow health care workers to apply risk reduction interventions to prevent - or at least minimize - the harmful effects of alcohol use during pregnancy in the newborn. Moreover, biomarkers may facilitate the diagnosis of FASD, which is not always straightforward due to the varying clinical presentation of FASD in newborns and children. Currently, several biomarkers have been studied for the detection of maternal alcohol exposure. When choosing which biomarker to use, several factors should be taken into account, including whether one wants to identify short-term vs. long-term alcohol use, the magnitude and timing of alcohol use to be identified and the desired sensitivity and specificity of the marker. In the following paragraph, we briefly describe currently available biomarkers.

Direct measurement of alcohol in blood, exhaled air or urine is considered the gold standard for the detection of alcohol use. However, the diagnostic yield of these tests is limited by the short half-life of alcohol (only a few hours). Indirect markers such as liver tests (including gamma-glutamyltransferase) and mean corpuscular volume can be chosen in cases involving chronic excessive alcohol use, but these methods lack

acceptable sensitivity and specificity. Carbohydrate deficient transferrin (CDT) is an iron transporter protein that can be detected in serum to assess moderate to excessive alcohol use in the 2-4 weeks prior to measurement. Improvements in analytical techniques to quantify serum CDT levels may have increased its diagnostic accuracy. However, its specificity remains suboptimal, and its use in pregnancy is still controversial because of the concern that CDT can be affected by a number of maternal conditions such as advanced gestational age, iron deficiency, and hypertension.

Direct alcohol metabolites, including ethyl glucuronide (EtG), ethyl sulfate (EtS), fatty acid ethyl esters (FAEEs) and phosphatidylethanol (PEth) are highly specific and, in general, have a wider time window of detection than alcohol itself (Figure 5).

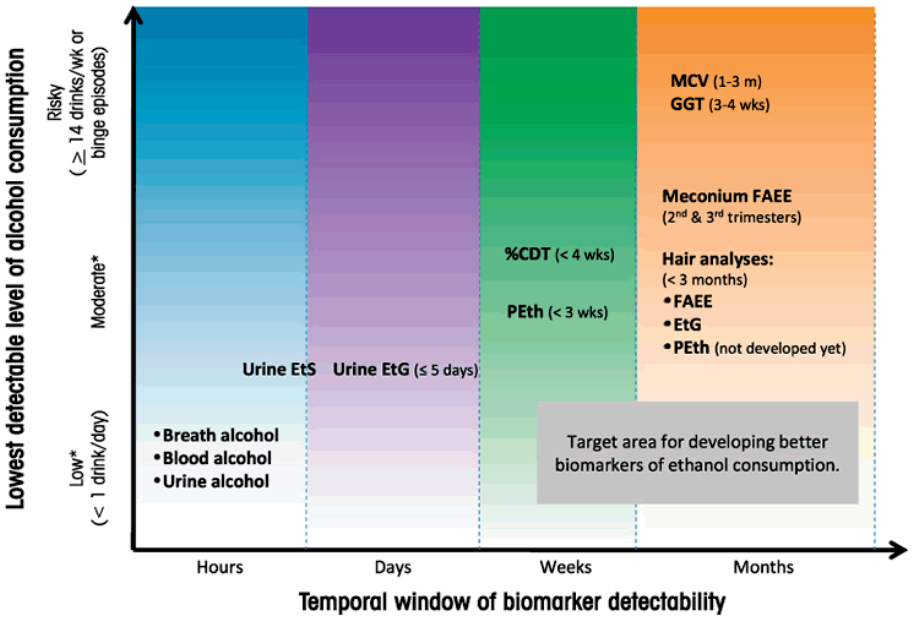

Figure 5 Temporal Window of Biomarker Detectability vs. Lowest Detectable Level of Alcohol Consumption. EtS: Ethyl Sulfate, EtG: Ethyl Glucuronide, % CDT: Carbohydrate-Deficient Transferrin, PEth: Phosphatidylethanol, MCV: Mean Corpuscular Volume, GGT: Gamma-Glutamyltranspeptidase, FAEE: Fatty Acid Ethyl Esters. *the Definition of Low and Moderate Drinking in Pregnant Women Varies Greatly Among Studies. Source: Bakhireva & Savage (2011) [60]

In recent years, **EtG** has gained attention as an acceptable biomarker of alcohol consumption, mainly in the forensic literature. EtG is the product of the glucuronization of alcohol in the hepatocyte, and can be detected in blood (with only a short half-life of several hours), urine, hair and meconium. Urinary EtG has been described as a highly sensitive biomarker for the detection of alcohol use, but only provides information on alcohol use in the previous 48 to 72 hours, and may be positive after accidental consumption of foods containing alcohol. EtG in scalp hair (hEtG) is a highly sensitive and

specific biomarker for the detection of chronic and excessive alcohol use. The hEtG concentration in the proximal 3 cm hair length correlates with the consumed amount of alcohol over the last 3 months in both alcohol-dependent and healthy individuals. With this large diagnostic window, hEtG would be an ideal biomarker to accurately assess alcohol intake in pregnant women, as compared to biomarkers measured in more traditional biological matrices such as blood and urine. However, hEtG allows no discrimination between abstinence on the one hand, and occasional or moderate use (or even intermittent binge drinking) on the other hand. This is a limitation, as even low amounts of alcohol use during pregnancy may lead to FASD. Meconium EtG might be more sensitive than hEtG. EtG possibly crosses the placenta and thus EtG in meconium may reflect both fetal and maternal metabolism. **EtS** is another direct, non-oxidative product of alcohol metabolism that can be measured in blood, urine, hair, and meconium. However, EtG is the more reliable of the two with regard to serum, has a longer detection period in urine, is more sensitive in meconium, and is more commonly used.

Fatty acid ethyl esters **(FAEE)** are produced by the esterification of alcohol with fatty acids, triglycerides, lipoproteins and phospholipids, and can be found in meconium, hair, and blood. FAEE cannot pass the placenta. Thus, FAEE in the meconium are synthesized by the fetus from alcohol that has crossed the placenta. The formation of meconium starts from a gestational age of 12-18 weeks. Therefore, FAEE in the meconium represents the cumulative alcohol use in the second (when the formation of meconium starts) and third trimester of the pregnancy. Sensitivity decreases at moderate-to-low levels of alcohol exposure. FAEEs have been detected in meconium from infants of women who did not consume alcohol in pregnancy, but at much lower levels than among women who did. A disadvantage of the analysis of meconium (this also applies to EtG in meconium) is that the test result is only available after pregnancy. FAEE can also be detected in hair but this approach is less well validated than hEtG. FAEE in blood can show alcohol exposure within 1 or 2 days, depending upon the magnitude of exposure.

PEth is a unique phospholipid that is only formed by the interaction of alcohol with phosphatidylcholine catalyzed by phospholipase D in red blood-cell membranes. It can be detected in blood for several weeks following low-to-moderate prenatal alcohol consumption.

Biomarkers used for risk assessment and for the diagnosis of FASD

It is important to understand the relationship between maternal alcohol exposure and susceptibility to developing FASD in the offspring. Therefore, in addition to biomarkers of maternal alcohol use, we need markers to diagnose FASD without recourse to time-consuming and expensive clinical diagnostic procedures. This latter research area is in

its infancy, but some promising results have been published. For example, with regard to prenatal diagnosis, a recent report demonstrated that infants who were identified as alcohol-affected at birth could be predicted by microRNA (miRNA) profiles in the maternal blood as early as the second trimester (3 to 6 months) of pregnancy [61]. Other work has focused on the use of second trimester ultrasound for the early detection of children with FASD [62]. As for diagnosis in early infancy, research has focused on phenomena such as cardiac orienting responses [63] and eye-tracking [64].

Given the current state of knowledge about the long-term effects of prenatal alcohol exposure, it should be possible to identify biomarkers that reflect the physiological changes occurring in persons with FASD, even later in childhood or adulthood, such as proteins or lipids modified by ROS. Such biomarkers have been identified in cell lines [65], but have not yet been sufficiently studied for application in human studies or in the clinic.

Conclusion and future perspectives

FASD is caused by prenatal alcohol exposure and is therefore entirely preventable. Despite growing research efforts, a gold standard either to confirm long-term abstinence or to detect alcohol use is currently lacking. All the above-mentioned methods have their limitations, and the reported accuracies of biomarkers of alcohol use vary widely across studies. The ideal biomarker would: 1) be able to detect low-to-moderate levels of drinking over extended periods of time; (2) be able to accurately detect drinking that has occurred during pregnancy (i.e., high sensitivity); (3) have a low rate of false-positive test results (i.e., high specificity) and (4) require a biological sample which can be obtained with minimally invasive methods [60]. Currently, none of the available biomarkers fulfill all of these requirements, and current evidence is insufficient to support the use of objective measures of prenatal alcohol exposure in practice. Before clinical implementation, further validation of the current biomarkers (or a combination thereof) is required. More specifically, the use of the proposed cut-off levels to categorize pregnant women into different drinking groups and the correlation of the test result with the consumed amount of alcohol should be assessed. In addition, longitudinal studies should assess the duration of abstinence required for a positive test outcome to become negative. This is of major importance for the interpretation of a single test result in order to either detect alcohol relapse or confirm sustained abstinence.

Thus far, biomarkers have not often been used for diagnosis. There is a need to develop biomarkers that can be used for prenatal diagnosis, which would allow for early intervention to minimize the long-term effects of prenatal exposure. In addition, it should be possible to identify biomarkers of the long-term physiological changes that extend into adulthood.

In parallel with gaining further insight into the pathophysiology of FASD, research on new biomarkers in different sampling matrices is required. Future biomarkers may be derived from genomic, transcriptomic, proteomic and metabolomic in-depth analyses in pregnant women consuming alcohol. Ideally, we would like to have markers of fetal effects, and not just merely of alcohol exposure. It would also be interesting to explore the predictive value of alcohol biomarker levels in pregnant women in order to identify future adverse neurodevelopmental outcomes in children.

In conclusion, given the serious consequences of prenatal exposure to alcohol, the following types of biomarkers are urgently needed: biomarkers of alcohol consumption during pregnancy, biomarkers for diagnosis during the pregnancy or at birth, and biomarkers that could be used for diagnosis later in childhood or adulthood.

2.5. Genetic Factors and Alcohol Consumption

Current knowledge

Identifying genetic determinants of drinking patterns may also help to identify biological mechanisms contributing to specific drinking patterns, and to identify women at risk of (high) alcohol consumption. Prevention strategies for moderating and stopping alcohol consumption in women both before and during pregnancy could target these biological mechanisms and could be directed towards individuals at high risk of alcohol consumption and abuse due to genetic predisposition.

Putative genetic underpinnings of drinking patterns include markers of alcohol consumption and dependence identified in genome-wide association studies (GWAS), markers of bitter taste perception, and markers of alcohol tolerance. To date, most research into the genetics of alcohol consumption has focused on genetic markers of alcohol dependence (see the GWAS catalog at www.ebi.ac.uk/gwas/). The maximum number drinks consumed in 24 hours is a characteristic that is strongly correlated with alcohol consumption and dependence in individuals who drink alcohol, and this characteristic has been shown to be heritable (approximately 50%) [66]. Very few studies have investigated markers of alcohol consumption at the lower end of the intake level, the moderate consumption level, which is common to many individuals in many societies. Moderate drinkers are difficult to distinguish from those with alcohol dependence in most studies. Variation in the glycosylation of transferrin has been studied extensively because the concentration or proportion of less-glycosylated transferrin, referred to as carbohydrate-deficient transferrin (CDT), can serve as a biomarker of excessive alcohol consumption. The top three SNPs from GWAS associated with CDT have been observed in SNPs annotated to the transferrin gene (*TF*) and the phosphoglucomutase-1 gene (*PGM1*) [67]. In a recent Swedish study[68], two single nucleotide polymorphisms (SNPs) in *CNTN4* (contactin 4) were replicated in relation to self-

reported regular alcohol consumption in two observational studies, although a distinction between regular alcohol consumption and alcohol dependence was not made. Since *CNTN4* has been linked to olfaction and development of olfactory neurons [69], it can be speculated that taste preference for alcohol could act as a mechanism through which *CNTN4* could influence drinking.

Genetic markers of bitter taste perception are of interest in relation to bitter-tasting alcoholic beverages such as beer and certain types of liquor. Bitter taste perception has been attributed to the taste 2 receptor (*TAS2R)* gene cluster; in particular *TAS2R38* haplotypes have been demonstrated to clearly distinguish between non-tasters, medium-tasters, and super-tasters of bitter taste [70]. Since many naturally occurring toxic compounds confer a bitter taste, bitter taste is thought to evoke aversion in humans, avoiding ingestion. Thus, non-tasters have been found to consume more alcohol than tasters in some studies[71–73], though not all [74,75]. Null findings may be explained by the fact that total alcohol intake was investigated in these studies instead of specific bitter-tasting alcoholic beverages, such as beer. *TAS2R38* non-tasters as compared to tasters have been found to be at an increased risk of alcohol-associated diseases such as colorectal cancer, [76] but have not been investigated in relation to FASD.

Genetic markers of alcohol tolerance in the alcohol- and acetaldehyde-dehydrogenase (*ADH* and *ALDH*) gene family, which is responsible for ethanol metabolism, can severely diminish an individual's tolerance to alcohol and thereby determine drinking patterns and risk of FASD. Alcohol metabolism mainly occurs in the liver, where ADH enzymes oxidize alcohol (i.e., ethanol) to the toxic acetaldehyde, and ALDH enzymes oxidize the acetaldehyde to acetate. Functional studies have been carried out on *ADH1B* and *ADH1C* gene variants [77]. For *ALDH2*, two alleles exist, one of which has a very low activity, resulting in acetaldehyde accumulation after alcohol consumption; this genetic variant is largely absent in most Caucasian individuals [77].

Knowledge gaps

Future research should investigate the role of genetic markers of alcohol consumption in relation to FASD at lower levels of alcohol intake.

Recommendations

There is a paucity of studies investigating the genetic determinants of moderate alcohol consumption. The role of genetic markers of alcohol consumption has never been investigated specifically in relation to FASD at lower levels of alcohol intake. A Mendelian-Randomization approach, using polygenic risk scores[78], could be of use to further investigate and understand FASD at lower levels of alcohol intake. Such approaches would require studies with large sample sizes [78]. It is likely that this kind of future

genotype research will result in a better understanding of an individual's risk of having a child with FASD.

2.6. Maternity Care

In terms of maternity care, obstetricians and midwives are important stakeholders. In the Netherlands, maternity care is organized within a primary, secondary and tertiary care model. Primary care is provided by midwives and *general practitioners* (GPs). GPs are responsible for only about 0.5% of all births, mainly in rural areas with a low population density. Other professionals who are active within primary care include mental healthcare professionals, maternity care workers, and professionals in 'neighborhood teams'. Secondary care consists of obstetricians and specialized 'clinical' midwives in general hospitals, and tertiary care comprises obstetricians in academic hospitals [41,79].

Important steps that can be taken in order to improve maternal care include reducing risk factors such as stress, alcohol, smoking, nutrition, and overweight, and addressing their underlying mechanisms [80]. Moreover, in order to make improvements in terms of prevention and care around pregnancy and birth, it is important to strengthen the existing knowledge infrastructure and to stimulate multidisciplinary research [41,80].

In the following sections, maternity care will be described from the perspectives of obstetrics, gynecology and midwifery.

Obstetrics and gynecology

Current knowledge

In the Netherlands, the National Scientific Association of Gynecologists (NVOG) monitors the general health of women - in particular their gynecological, obstetric, and reproductive health. The association provides patients and their relatives with important information regarding these areas of health. With respect to alcohol consumption during pregnancy, the NVOG's advice for their members is based upon information provided by the Dutch Health Council [38]. The National Steering Group GGZ Netherlands also incorporates this advice in their guidelines on alcohol use and pregnancy [81]. The Dutch Health Council recommends that women and their partners discontinue alcohol use as soon as they plan a pregnancy. The committee of the Health Council formulates it as follows:

"The Committee's conclusion is that it is not possible to determine a male and female lower limit for alcohol consumption prior to conception from which it could definitely be said that there was no effect upon on fertility and pregnancy." Dutch Health Council, 2005. [38]

"The Committee concludes that every reduction in alcohol consumption leads to a reduction in risks. It is not possible to determine a lower limit for alcohol consumption from which it can be stated with certainty that there would be no effect on the fetus and the pregnancy." Dutch Health Council, 2005. [38]

"The conclusion is that it is not possible to indicate a safe lower limit for alcohol consumption during breastfeeding." Dutch Health Council, 2005. [38]

In agreement with this 2005 recommendation of the Health Council, in 2007 the committee advised professionals to discuss the topic of alcohol use [using neutrally formulated questions and in a systematic way] with prospective pregnant women and their partners, and to recommend that any alcohol use is discontinued as soon as they want to fall pregnant [24]. As long as there is no known safe limit, the health council advises potential parents not to use alcohol at all.

In practice, most women only stop using alcohol as soon as a pregnancy test is positive. This might mean that the woman is already more than 2 weeks pregnant.

A good example of how to build consensus and develop strategies for improving preconception care is the ZonMw program 'Zwangerschap en Geboorte' ('Pregnancy and Birth') [41]. This program comprises seven projects with a focus on preconception care. These projects target expectant parents and are designed to stimulate health care professionals to improve preconception care and make parents more aware about maintaining a healthy lifestyle (e.g., by not drinking alcohol during the preconception period and during pregnancy). For example, one of these projects, the APROPOS Preconception Care project, uses a tailored preconception care approach directed towards couples who wish to pursue healthy (pre-) pregnancy behavior (see http://www.zwangerwordeninzeist.nl).

The ZonMw program 'Pregnancy and Birth' was designed to improve existing knowledge infrastructures for maternity care by encouraging cooperation between various professional disciplines involved in maternity care and establishing regional consortia. One example of this is the Limburg Obstetric Quality System (LOQS) for women experiencing problems in pregnancy) [41].

Knowledge gaps

In the Netherlands, there are no reliable data regarding alcohol consumption by pregnant women (before and during pregnancy). During initial (intake) interviews with pregnant women the gynecologist does not usually pay much attention to the use of alcohol; some do not ask the question at all, others believe it is confrontational to ask in-depth questions about alcohol intake.

"Mosos" is a software program designed to maximize best practice in obstetrics. The development of Mosos was undertaken in close cooperation with gynecologists, mid-

wives, universities and government agencies. It is the software program most frequently used by gynecologists. Perined is a Dutch foundation responsible for perinatal audit and registration. This foundation consists of four professional organizations which work together and are responsible for all aspects of maternal and child health care; KNOV (Koninklijke Nederlandse Organisatie van Verloskundigen), LHV (Landelijke Huisartsen Vereniging) including GPs who practice midwifery united in the VVAH (De Vereniging van Verloskundig Actieve Huisartsen), NVOG (Nederlandse Vereniging voor Obstetrie en Gynaecologie), NVK (Nederlandse Vereniging voor Kindergeneeskunde) and NVVP (Nederlandse Vereniging voor Pathologie).

Currently, these software programs do not allow in-depth questions to be asked concerning alcohol use. For instance, Mosos allows the user (under the heading of anamneses) to complete questions about alcohol use. However, the physician can only choose between four answer options: "no," "unknown," "many," "few: 1 / week". It is not possible to differentiate between - for instance - trimesters of pregnancy.

Recommendations

We recommend to use the existing infrastructure for maternity care through stimulating transcend occupations as provided among others in the ZonMw program Pregnancy and Birth [41] and the program “Transitie Geboortezorg” (Program Transition Birth Care; https://www.transitiegeboortezorg.nl).

A system such as “Mosos” can contribute to the monitoring of alcohol use among pregnant women. Questions such as “did you consume alcohol prior to conception?”, “did you consume alcohol during conception?”, and “how much alcohol did you consume?” could be considered for inclusion. These questions should be asked for preconception and for the first, second, and third trimesters of pregnancy. In addition to timing (when), frequency (how often) and amount (how much) should be specified.

The data collected via “Mosos”, combined with data from in-depth interviews, and alongside information regarding the distribution of the sample across the Netherlands, gives us some idea about the scope of the problem.

Midwifery

Current knowledge

Midwives in the Netherlands are registered with the Royal Dutch Organization of Midwives (*KNOV,* Koninklijke Nederlandse Organisatie van Verloskundigen). They are the case managers during pregnancy, childbirth and the post-partum period.

The KNOV, like the NVOG, follows the recommendation of the Dutch Health Council - that alcohol should not be used at all during pregnancy [38].

Knowledge gaps

For midwives (as well as obstetricians and gynecologists), discussing alcohol consumption with their patients appears to be difficult and is not a top priority. Intervention programs in which alcohol use during pregnancy is discussed are scarce. Exceptions include an e-learning module [82] and a brief health counselling program [83].

Recommendations

Midwives have a prolonged and intensive contact with (future) mothers and are therefore important stakeholders. There is a need for further training for midwives with regard to screening for alcohol use and the implementation of brief intervention measures related to alcohol consumption (where indicated).

Most higher educated women are able to find and maintain contact with a midwife without encountering problems. Missed target groups for receiving midwife care include women of low socioeconomic status (SES) and individuals with substance abuse problems. It is therefore necessary to develop strategies to get in touch with these target groups.

In addition, intervention programs designed to be implemented by midwives should be evaluated for their effectiveness.

2.7. Prevalence of FASD

Current knowledge

The first systematic publications mentioning the harmful effects of prenatal alcohol exposure comprised a series of case studies of children born to alcoholic mothers published in 1968 by Lemoine and colleagues in France. In 1973, Jones and Smit published a paper in the Lancet on the same topic. In contrast to the publication by Lemoine et al., this paper received international attention [29,30]. Various epidemiological studies have been conducted worldwide to estimate the prevalence of FASD. Since FASD is a birth defect, using the term ”incidence” is not appropriate [84,85].

Roozen et al. recently researched worldwide prevalence estimates of FASD in order to produce a systematic literature review and meta-analysis [85]. Data revealed that prevalence rates were available for only seven countries (see Table 1). Prevalence rates were sampled from the general population and from suspected high-prevalence subpopulations. Prevalence estimates from suspected high-prevalence subpopulations were not included in the meta-analysis, as these rates are biased upwards due to the sample selection. Reported prevalence estimates displayed considerable heterogeneity, which was largely explained by country and descent. In meta-analyses per country, descent, case ascertainment method, and age range also emerged as moderators. On

the basis of the findings of studies that sampled the general population (conducted in Australia, Canada, Croatia, Italy, New Zealand, South Africa, and the United States), the pooled prevalence rates were particularly high in South Africa for FAS (55.42 per 1,000), ARND (20.25 per 1,000) and FASD (113.22 per 1,000). For pFAS, high rates were found in Croatia (43.01 per 1,000), Italy (36.89 per 1,000), and South Africa (28.29 per 1,000). In the case of ARBD, a prevalence of 10.82 per 1,000 was found in Australia. Recent rates were published in the Lancet by Popova and colleagues [42]. The authors estimated global FAS prevalence rates to be 14.6 per 10,000 livebirths and FAS prevalence rates in Europe to be 37.4 per 10,000 livebirths. These figures should, however, be interpreted with caution, given the limitations of the study. For the Netherlands, there are no FASD prevalence data available.

Table 1 Meta-Regressions for Global and Local FASD Prevalence Estimates

	FAS	pFAS	ARND	ARBD	FASD
Global prevalence	$2.89_{k=94}$ [0 to 39.65]	$11.22_{k=17}$ [0 to 76.12]	$5.19_{K=6}$ [0 to 54.2]	$3.52_{k=5}$ [0 to 17.81]	$22.77_{k=13}$ [0 to 176.77]
Local prevalence					
Australia	$1.33_{k=11}$, [0 to 37.61]	$0.8_{k=3}$, [0 to 6.3]	$0.12_{k=2}$, [0 to 1.76]	$10.82_{k=1}$, [[8.05 to 13.99]]	$1.06_{k=6}$, [0 to 10.05]
Canada	$37.19_{k=3}$, [0 to 398.08]				$30.52_{k=2}$, [23.81 to 38.04]
Croatia	$11.73_{k=2}$, [1.23 to 31.26]	$43.01_{k=2}$, [25.41 to 64.85]			
Italy	$8.2_{k=1}$, [[3.35 to 14.99]]	$36.89_{k=1}$, [[25.9 to 49.69]]	$1.03_{k=1}$, [[0 to 4.4]]	$1.03_{k=1}$, [[0 to 4.4]]	$47.13_{k=1}$, [[34.66 to 61.38]]
New Zealand	$0.11_{k=1}$, [[0.08 to 0.13]]				
South Africa	$55.42_{k=8}$, [18.42 to 110.38]	$28.29_{k=5}$, [0 to 108.22]	$20.25_{k=2}$, [0 to 148.23]		$113.22_{k=3}$, [7.04 to 319.21]
United States	$0.67_{k=68}$, [0 to 5.44]	$2.22_{k=6}$, [0 to 17.09]	$9.07_{k=1}$, [[4.73 to 14.73]]	$2.58_{k=3}$, [0 to 15.79]	$33.5_{k=1}$, [[24.76 to 43.48]]

Source: Roozen et al. (2016) [85]. *Note*. This table represents global FASD prevalence estimates including the associated prediction intervals followed by local FASD prevalence estimates whereby *k* is the number of samples. Double brackets signify confidence intervals (as opposed to prediction intervals).

Knowledge gaps

There is currently no reliable means of estimating the prevalence rates of FASD in most countries, including the Netherlands. Surveillance studies of FASD using multiple sources are not available for the Netherlands. Moreover, hardly any cases of children with FASD are reported to the Dutch Surveillance Center for Pediatricians (NSCK), although there are studies available in the Netherlands about FASD cases. In 2012, the NSCK published a report consisting of an overview of problems identified over the past 20 years by pediatricians [87]. This report included a limited number of cases involving

the suspicion of FAS or pFAS. The diagnoses were, for most of these cases, requested by adoptive or foster parents. Abdelmalik and colleagues (2013) studied a cohort of 27 children suspected of having FASD, who were referred to the Academic Medical Center (AMC) in Amsterdam [88]. When FASD diagnostic guidelines (e.g., 4-Digit, IOM guidelines, see paragraph 3.2) were applied, 11 out of 27 patients received a FASD diagnosis. Swelheim, Flapper, and Van Balkom summarized data collected from the FASD outpatient center in Groningen, the Netherlands, between 2009 and 2012 [89]. During this period, 151 children were registered at the FASD clinic. Most of these children were referred by Youth Healthcare Centers. Using the 4-Digit guidelines, FASD was diagnosed in 112 of these children (57 mild FAS, 55 pFAS).

In the Netherlands, FASD is flagged by professionals working in different disciplines (including pediatrics, genetics, and child psychiatry), and sometimes by those working in specialized FASD outpatient clinics. As cases are not recorded via a structured surveillance system, there is no reliable evidence available on FASD prevalence in the Netherlands. There is, therefore, a need to better understand the current scope of the problem in the Netherlands.

Recommendations

Further epidemiological research is needed in order to establish prevalence rates. This research should include active case ascertainment (whereby researchers collect data in the field e.g., at schools); passive surveillance (whereby researchers inspect existing records); and clinic-based surveillance (whereby researchers examine consenting mother-newborn dyads following childbirth) [85]. Prevalence estimates can be calculated from the number of existing cases at a given point in time using equation 3 provided by Mason and colleagues : prevalence = 10^3 multiplied by the number of cases divided by the total number of live births [84,85].

It is important to determine populations at risk and to use uniform diagnostic criteria for diagnosing FASD. The same recommendations for calculating prevalence rates as published in the 2016 British Medical Association (BMA) report for the UK [15] can also be followed in the Netherlands. The World Health Organization (WHO) is currently planning prevalence studies in several countries across Europe, Asia, Africa, and North America, which should lead to more global data about the frequency of this continuum of disabilities becoming available [14]. For the Netherlands, there is a need for reliable national FASD prevalence estimates to be established. We recommend exploring the possibilities of collecting data from existing databases (e.g., Perined, NSCK, NVK for pediatricians).

2.8. Risk Behaviors

Current knowledge

In order to develop health promoting programs aimed at reducing alcohol consumption during pregnancy, it is necessary to identify which specific prenatal alcohol drinking behavior(s) are most in need of intervention.

Roozen et al. [90] conducted the first systematic literature review summarizing available data from studies reporting maternal alcohol drinking behaviors related to FASD (see Table A1 in the Appendix). The majority of the studies (*n* = 20) were based on retrospective self-reports or interviews with mothers of children diagnosed within the spectrum of FASD. Studies used both objective measures (numerical datatypes) and subjective measures (dichotomous and ordinal datatypes). Variables of maternal drinking behavior displayed substantial variation which precluded further aggregation and meta-analysis. Please refer to Table 2 for examples of variables and of how studies reported maternal alcohol drinking behaviors using dichotomous (e.g., alcohol consumption yes or no), nominal (e.g., alcohol consumption admitted, negative, unanswered), ordinal (e.g., <4 drinks, >4 drinks), or continuous data type (e.g., number of drinks in mg, g, or oz) measures.

Based on the available studies, substantial heterogeneity in the methods used to measure alcohol consumption was observed and precludes further conclusions being drawn about the relationship between maternal alcohol consumption and the likelihood of infants developing FASD. One of the reasons for this heterogeneity is that none of the studies included in the analysis was conducted primarily to investigate the association between maternal drinking behavior and FASD. Although both variables were frequently measured and reported, most studies were designed to determine prevalence or FASD symptoms.

Table 3 shows the percentages of women in the Netherlands consuming alcohol during their pregnancy. Further details on specific maternal alcohol drinking behaviors (e.g., drinking patterns before pregnancy, frequency of occasions when alcohol is consumed, and amount of alcohol per occasion), as well as data on educational attainment, are available for the following studies: Jentink and colleagues (2011) [91], Lanting and colleagues (2015) [40], and Lanting and colleagues (2015) [39].

Table 2 Examples of how Variables on Maternal Alcohol Drinking Behaviors are Reported in Different Studies

Measurement levels	Variables
Dichotomous	Before pregnancy • Drank alcohol before pregnancy (yes/no) • Abstained from alcohol (yes/no) • Drank low amounts of alcohol (yes/no) • Drank moderate amounts of alcohol (yes/no) During pregnancy • Alcoholism (yes/ no) • Binge drinking (yes/no) • Binge drank 3 or more drinks per occasion (yes/no) • Binge drank 5 or more drinks per occasion (yes/no) • Drank alcohol during pregnancy (yes/no) 1st trimester pregnancy • Drank alcohol during first trimester pregnancy (yes/no) • Abstained from alcohol (yes/no) • Drank low amounts of alcohol (yes/no) • Drank moderate amounts of alcohol (yes/no) 2nd trimester pregnancy • Drank alcohol during second trimester pregnancy (yes/no) • Abstained from alcohol (yes/no) • Drank low amounts of alcohol (yes/no) • Drank moderate amounts of alcohol (yes/no) 3rd trimester pregnancy • Drank alcohol during third trimester pregnancy (yes/no) • Drank alcohol during late pregnancy (yes/no)
Nominal	During pregnancy • Drank alcohol during pregnancy (admitted, negative, unanswered)
Ordinal	Before pregnancy • Drinking: abstinent (0 g/week), mild (0-20 g/week), moderate (20-80 g/week), heavy (>80 g/week) • Drank about the same compared to current use, drank less, drank more, did not drink, stopped during this period, drank during index pregnancy During pregnancy • Drinks during one sitting (<4 drinks, >4 drinks) • Number of drinking days per week (<7 days, >7 days) • Drinking: abstinent (0 g/week), mild (0-20 g/week), moderate (20-80 g/week), heavy (>80 g/week) • Drinks per week (0, 1-3, 4-6, 7-12, 13-20, 21-98, >98, unknown) 1st trimester pregnancy • Drinking: abstinent, low (<70g and on one day no more than 2 standard drinks), moderate (<70g alcohol per week and 21 to 49g per occasion), moderate and binge drank less than weekly, heavy and binge drank 1 or 2 times a week, heavy and binge drank >2 times a week, heavy (<50g per occasion so no binge drinking, 70.1-140.0g a week), very heavy (<50g per occasion so no binge drinking, > 140.1g a week) • Drank about the same as compared to current use, drank less, drank more, did not drink, stopped during this period, drank during index pregnancy 2nd trimester pregnancy • Drank about the same compared to current use, drank less, drank more, did not drink, stopped during this period, drank during index pregnancy 3rd trimester pregnancy • Drank about the same as compared to current use, drank less, drank more, did not drink, stopped during this period, drank during index pregnancy

Measurement levels	Variables
Continuous	Before pregnancy • Number of drinks per day • Number of drinks per week During pregnancy • Number of drinks per week • Number of drinks during a drinking day • Number of drinks Monday-Thursday • Number of drinking days per week • Alcohol consumption • Alcohol consumption during an occasion 1st trimester pregnancy • Number of drinks • Peak estimated Blood Alcohol Content (BAC; mean, SD) 2nd trimester pregnancy • Number of drinks • Peak estimated BAC (mean, SD) 3rd trimester pregnancy • Number of drinks • Peak estimated BAC (mean, SD)

Table 3 Overview of Studies Measuring Alcohol Consumption Among Dutch Pregnant Women

Author	Sample Year	Sample Area	Sample Size	Assessment Method	Alcohol consumption during pregnancy (%)
Verkerk and colleagues (1993) [92]	1978-1979	Various regions (midwife centers; EUROMAC study)	2803-2901	Interview	78% (1st trimester) 51% (2nd trimester) 54% (3rd trimester)
Knottnerus and colleagues (1990) [93]	1985-1986	Maastricht (hospital, midwife centers)	796	Questionnaire	22%
Vonsee and colleagues (1989) [94]	1985-1987	Maastricht, Heerlen (hospital)	691 patients with specimens of trachomatis, 688 with hominis, and 639 with urealyticum	*NA*	1% 12% 65%
Tholen (1987) [38]	1987	Drenthe (obstetric practice)	142	Questionnaire	35%
Lanting and colleagues (2009) [95]	2001-2007	Nationwide	14.553	Questionnaire	28,6% (1st trimester) 24.3% (2nd, 3rd trimester)
Bakker and colleagues (2010) [96]	2002-2006	Rotterdam (Generation R study)	7333	Questionnaire	50% 13.4% (stopped after pregnancy recognition) 36.9% (continued throughout pregnancy)
Goedhart and colleagues (2008) [97]	2003-2004	Amsterdam (ABCD study)	3859	Questionnaire (online)	29.5%
Pfinder and colleagues (2013) [98]	2003-2004	Amsterdam (ABCD study)	5238	Interview	41,8% (non-daily drinker 36.%; daily drinker 5.6%)
Jentink and colleagues (2011) [91]	2004-2009	Veendam, Groningen (midwife centers)	529 (healthy pregnancy) 1839 (pregnancy with diagnosis of malformations)	Questionnaire	20.2% 28.6%
Mutsaerts and colleagues (2014) [99]	2006-2007	Drenthe (GECKO study)	2209	Questionnaire	4%

Author	Sample Year	Sample Area	Sample Size	Assessment Method	Alcohol consumption during pregnancy (%)
Smidts and Oosterlaan (2007) [100]	*NA*	Nationwide (pre- and primary schools)	652	Questionnaire	16.1%
Lanting and colleagues (2015) [40]	2007	Nationwide (Well-Baby Clinics)	2715	Questionnaire	22.4% 16.5% (1st trimester)
Kuppens and colleagues (2010) [101]	*NA*	Eindhoven (midwife centers)	1058	*NA*	12.9%
Lanting and colleagues (2015) [40]	2010	Nation-wide (Well-Baby Clinics)	1410	Questionnaire	19.2% 13.8% (1st trimester)
Beijers and colleagues (2014) [102]	2011-2013	Nationwide (hospital, midwife centers; PAD study)	1340	Questionnaire (online)	8.2%
Lanting and colleagues (2015) [39]	2015	Nationwide	1727	Questionnaire (online)	8.9% 6.9% (1st trimester) 3.2% (2nd, 3rd trimester)

Note. Measuring maternal alcohol consumption was not always the primary objective of the studies. Abbreviation *NA* was mentioned if the data could not be extracted from the publication.

Knowledge gaps

Current knowledge on maternal alcohol drinking behaviors in relation to FASD is limited. Behaviors have been measured using various techniques that have been operationalized in different ways. In order to develop evidence-based preventive measures, it is necessary to identify which prenatal alcohol drinking behavior(s) are most in need of intervention.

Most of the available studies were based on retrospective sampling methods. Often, data was obtained years after the child was born, risking biased recall of alcohol consumption patterns during pregnancy. Some studies used prospective sampling (e.g., Elliot et al., 2013) [103]. However, these studies were often designed to monitor the frequency of FASD and did not include variables on maternal alcohol drinking behaviors related to FASD.

In addition to these methodological shortcomings, none of the studies included in this review reported paternal drinking patterns or grandparental drinking patterns. The role of paternal drinking and transgenerational toxicity on fetal development and FASD is not well understood. A recent review study by Gupta and colleagues [45] reported that paternal alcoholism alters the gene expression for fetal susceptibility to FAS. Another review by Resendiz and colleagues (2013) [104] suggests a possible role of transgenerational toxicity in FASD etiology. Moreover, it has been shown that the impact of paternal drinking via social facilitation is significantly associated with maternal drinking [105]. The origin of FASD is therefore not only based on maternal drinking behaviors; many other factors play an important role (e.g., genetic and epigenetic predisposition, maternal body makeup, body mass index, and lifestyle). Gupta and colleagues (2016) [45] have emphasized that FAS, along with other diagnosis within the FASD spectrum, is based on a complex interaction of different factors, meaning that cautious interpretation regarding etiology is warranted [45].

Recommendations

Further research on maternal alcohol drinking behaviors in relation to FASD is needed.

For these studies, it is importance to pay close attention to the measurement of alcohol consumption patterns.

First, researchers should anticipate the need to aggregate their measures of alcohol consumption with measures from other studies: in other words, conversion to consumption in metric units, such as grams of alcohol, in a specified time period such as week or month, should be possible. If such conversion cannot be performed, the study cannot contribute to an accumulation of evidence. This recommendation translates into a number of specific suggestions. Most of these are covered by following guide-

lines for the measurement of alcohol consumption, such as those provided by Dawson (2003) [106] and Sobell and Sobell (1995) [107], but specifically, it is recommended that future studies assessing specific maternal drinking behaviors should, at the very least, report the following: (i) maternal characteristics (e.g., age), (ii) sample method, (iii) method used for maternal alcohol consumption assessment, (iv) timing of exposure (e.g., in which trimester), (v) frequency of exposure (e.g., number of exposure sessions per week or month), (vi) amount of alcohol consumed per exposure session, (vii) sample size including denominator, (viii) definition of one standard drink, (ix) quantification of alcohol measure (e.g., oz, g). Researchers should try to avoid discontinuous (categorical) measures, but if these are unavoidable, (x) the employed cut-offs must be clearly justified. Ideally, however, researchers would avoid self-report measures and instead use objective measures such as biomarkers collected by hair samples [58].

The second recommendation involves the inclusion of matched control groups based on maternal characteristics (e.g., age). When the control group is not matched, but, for example, all mothers with children who do not suffer from FASD are used, any associations that may be found between alcohol consumption and FASD are more likely to be confounded. For example, maternal age is positively associated to birth defects, and mothers from different social economic background may have different behavior patterns that also impact the likelihood of birth defects.

The third recommendation involves choosing an appropriate research design. Until now, most studies have used retrospective sampling methods. Often, data was obtained years after the child was born, risking biased recall of alcohol consumption patterns during pregnancy.

Fourth, maternal drinking is based upon a complex interaction of different factors - including genetic and epigenetic predisposition. Studies should not only focus on the role of maternal drinking but also on other factors such as, for instance, the role of paternal drinking and transgenerational toxicity on the development of FASD.

In short, the ideal design would comprise a large-scale prospective study in which maternal factors along with other factors influencing alcohol consumption would be assessed using both self-reports and objective measures (see also paragraph 2.3). Individuals would then be assessed for FASD as soon as possible and given an accurate diagnosis. Moreover, FASD prevalence would be assessed in relation to the alcohol consumption patterns of both parents separately and in conjunction. This design would also enable examination of potential confounding variables such as social economic status or age. Such an ideal design may not always be feasible. However, even when other designs are utilized, it is important that researchers anticipate the aggregation of data across studies, and therefore attempt to measure alcohol use in metric units.

Recommendations regarding advice (guidelines for behavior)

Some influential reports, for instance in the UK the BMA report published in 2016 and in the Netherlands the report published by the national Health Council in 2015 [108], advise women who are pregnant - or who may become pregnant - not to drink alcohol. So, abstinence is the recommended advice. This was formulated by the BMA 2016 as:

"There is no proven safe amount of alcohol that you can drink during pregnancy. It is also often difficult to work out just how much you are drinking, especially if you have a drink at home. The only way to be certain that your baby is not harmed by alcohol is not to drink at all during pregnancy or while breastfeeding" (p. 68) [15].

and in the Dutch Health Council report 2015 as:

"Voor vrouwen die zwanger willen worden, zwanger zijn of borstvoeding geven, luidt de aanbeveling om geen alcohol te gebruiken" (p. 59) [108].

Although the evidence regarding the negative effects of light drinking through to heavy drinking is conflicting and inconclusive (also in terms of drinking patterns and timing of exposure), different recommendations have been published by the WHO, the British Medical Association, and the Dutch Health Council. According to the WHO (2016), there is, despite individual vulnerability, no amount of alcohol which women can safely drink during pregnancy [43]. According to the BMA (2016), there are three different recommendations made by different UK national institutes [109]. First, the National Institute for Health and Care Excellence (2014) recommends women *not to consume any alcohol during the first three months of pregnancy (because there may be an increased risk of miscarriage), and that if women choose to drink alcohol during pregnancy they should be advised to drink no more than one to two UK units once or twice a week* [109]. Second, the Royal College of Obstetricians and Gynecologists (2015) advises women not to consume alcohol during pregnancy or while breastfeeding [109]. Third, the Department of Health, Social Services and Public Safety (2016) also recommends that women do not drink at all while pregnant [109]. The Dutch Health Council (2015) recommends complete abstinence for women who want to become pregnant, are pregnant, and women who breastfeed [108].

In conclusion, there is no known safe amount of alcohol to drink while pregnant and there is no new information which states otherwise. Binge drinking is one of the most serious risk factors and is associated with severe forms of FASD [110]. *Attention must be given to women who drink during pregnancy, with special focus on specific risk groups such as pregnant women who drink heavily (binge drink).* However, such a message should not overshadow the key message - not to consume alcohol during pregnancy or while breastfeeding.

2.9. Psychosocial Determinants of Maternal Drinking Behavior

Current knowledge

Theory. Changing something requires understanding it first. In the case of behavior change, it is necessary to understand why people engage (or do not engage) in the behavior of interest. These individual reasons, as far as they exist, are commonly conceptualized as ideas, cognitions, emotions, beliefs, processes, or automatic associations, etc. Behavioral determinants are generic aggregates of beliefs, which are specific to behavior, population, and context. It follows from this that we define personal determinants as generic, modifiable psychological variables or regulatory processes that are assumed, on the basis of empirical or theoretical evidence, to be causal antecedents of behavior [111].

Thus, a pregnant woman might believe that consuming alcohol will contribute to the enjoyment of the family dinner, or that it will help her cope with stress. She may reason that most of her friends drank a little whilst pregnant and that her health-care provider allows her a few drinks per occasion. The first two beliefs are generally thought to aggregate into the determinant *attitude*; the last two beliefs into the determinant *social norms*. Knowledge and risk perception are aspects of attitude but are often measured and reported separately. Beliefs underlying *self-efficacy* are different as they concern confidence, perceived ability and control. For example, a woman may feel confident that she can abstain from drinking alcohol and that she can resist offers of drinks. Attitudes, social norms and self-efficacy are so-called 'reasoned' determinants of behavior (they are not rational: people may have irrational reasons for their behavior), and together result in the *intention* for the behavior. A fourth type of determinant reflects *automatic, habitual and impulsive reactions*, which are less under volitional control and may override reasoned intentions [17].

This functional aggregation of similar beliefs into determinants has enabled the development of theories that can be used to explain a wide variety of behaviors in a wide variety of populations and contexts. Behavior change methods attempt to change behavior by trying to change determinants. However, as determinants are defined generically, they cannot be targeted directly. Instead, behavior change methods target specific beliefs, and therefore, for any behavior change method, it must be clear which belief(s) are targeted and into which determinant(s) these beliefs aggregate. It is, unfortunately, very common in descriptions of behavior change interventions in the scientific literature not to include (or to include only cursory) descriptions of the determinants targeted by the intervention. With no determinants specified, it is impossible for a reader to judge whether the theory-based change methods chosen to influence behavior are the most appropriate ones [17].

Evidence. Various studies have tried to quantitatively identify determinants of alcohol consumption by pregnant women, sometimes measuring dichotomous variables such as absolute drinking vs not-drinking, sometimes relative, i.e. amount of drinking. Their findings are summarized in Table 4.

Table 4 Psychosocial Determinants of Maternal Drinking (*= reverse effect)

1. Attitude	*No association with:*
1.1 Knowledge	x Having heard of FAS [112,113]
1.2 Risk perception	✓ Alcohol can harm the unborn baby* [113–117] • Risk – likelihood* [118], severity* [118] • Brain damage* [118] • Life-long disabilities for the child* [116] • Mental retardation* [112] • Alcohol has no effect on the baby [119] ✓ Only larger amounts of alcohol will harm the baby [119,120] • Some alcohol is acceptable [121–123] • Higher alcohol quantities judged as reasonable [124] • Any drinking is harmful* [119], abstinence is reasonable* [125] ✓ It is never too late to stop drinking* [125] *No association with:* x Binge drinking is harmful [122]
1.3 Outcome expectations/ Attitudinal beliefs	✓ I should reduce my alcohol intake during pregnancy* [123,126] ✓ Pregnant women should not drink* [116,122] ✓ Advantages (pros) of not drinking, e.g. baby's health* [118,127] ✓ Disadvantages (cons) of not-drinking, e.g. more stress [118,127] • Drinking can help with the pregnancy [120];
2. Perceived norms	✓ Partner norm: important not to drink*[118]
2.1 Subjective norms	✓ Partner support in not drinking* [118] ✓ Midwife's advice not to drink* [118] • Not received advice to stop drinking from HCWs or relatives [122,124] ✓ People speak about risks more with women who continued drinking [125] *No association with:* x Norms of significant others [127]
2.2 Descriptive norms	✓ Perceived partner modeling: partner does not drink in my presence* [118] ✓ Alcohol intake partner [118,123,124]; *no association* [122]
3. Self-efficacy/ perceived control	✓ Self-efficacy: confidence regarding abstaining* [127]; *no association* [128] • Can hold more than four drinks, indicating binge drinking [123] ✓ Being sad or discouraged in the last month [123] • Could use treatment at current time [123] • Abstinence messages made pregnant women feel negative about themselves [125] *No association with:* x Social self-efficacy, level of difficulty e.g. with friends [118] x Stress self-efficacy, level of difficulty e.g. when feeling sad [118]
4. Automatic, habitual & impulsive behavior	✓ Higher alcohol frequency before pregnancy [113,117,118,128] • Idem, only for smokers, not for non-smokers [127] • Idem, only frequency, not amount [117] ✓ Greater drinking during previous pregnancy [116,120] ✓ Difficulty remembering after drinking, [123]; ✓ Temptation – cue reactivity [128]

5. Intention	✓ I will reduce alcohol intake [126] *No association with:* x Binge drinking intention [126]
6. Distant determinants	✓ Smoking [124,127], however: smoking* [117]; *no association* [113,118] • Smoked during last pregnancy, [116] ; • Intend to smoke while pregnant, [116]; • Used drugs before pregnancy, [123]; ✓ Given birth previously [116,121]; no association with first pregnancy [117,118] • Complications last pregnancy* [118] • Previous abortion [123] • Lower rate of pregnancy planning [113] ✓ Sleep duration* [117] ✓ Sexual and physical abuse [123] ✓ Education [116–118,128]; however: education* [113] • Stopped school <16 [121] ✓ Age [118,121], age 30-39 highest [117]; *no association* [113,116] ✓ Full-time housewife* [123] ✓ Married* [123], no association [118] ✓ Lowest and highest income [123]; *no association* [113,118] *No association with:* x Employment [113]

Knowledge and risk perception. Simply having knowledge about the existence of FAS does not influence maternal drinking behavior. Most studies report a negative association between perceptions of the risk of maternal drinking for the unborn child and actual drinking behavior. However, risk perception beliefs that some alcohol is acceptable - and only higher amounts of drinking are harmful - are positively associated with maternal drinking. The belief that it is never too late to stop drinking is negatively associated with maternal drinking.

Attitudes. Attitudinal beliefs that pregnant women should not drink or should reduce their drinking, as well as recognizing the advantages of not-drinking for the baby's health, are negatively associated with maternal drinking. On the other hand, recognizing the disadvantages of not-drinking, such as an increase stress, and the belief that drinking can help with the pregnancy, are positively related to maternal drinking.

Social norms. Expectations and support from the partner for not drinking alcohol are negatively related to maternal drinking, as well as recommendations to stop drinking from midwives and other health care workers (not all health care workers give this advice; some even suggest that "having a glass of wine is actually better for the baby", i.e. Crawford-Williams et al., 2015) [129]. Expectations of others have no clear association with maternal drinking, possibly because those expectations are most likely communicated when women continue to drink whilst pregnant. The partner not drinking in the presence of the woman is negatively associated with maternal drinking. The partner consuming alcohol is repeatedly shown to be positively associated with maternal drinking, but not consistently.

Self-efficacy. Results concerning beliefs about self-efficacy for abstaining from alcohol consumption are mixed. In one study, beliefs about self-efficacy regarding not drinking have been shown to be negatively associated with maternal drinking, but in two other studies there was no association. However, women's beliefs related to being sad, discouraged, in need of help, and feeling negative about themselves, are positively related to maternal drinking.

Automaticity. Many studies find a positive association between drinking before pregnancy and drinking while pregnant; possibly more so for smokers, and only in relation to frequency of drinking, not the amount. Drinking during an earlier pregnancy is also positively associated with current maternal drinking. Women who have difficulties remembering after drinking also drink more often while pregnant. All these findings suggest that maternal drinking is partly a habitual behavior. Only one study measured cue-reactivity to alcohol as a measure of temptation to drink and showed a positive association between cue-reactivity and maternal drinking. This finding suggests that maternal drinking is, partly an impulse behavior. The situation is different when the mother is dependent on alcohol intake. In such cases, it is recommended that professional help is offered to address the dependency.

Intention. Pregnant women who have the intention to reduce alcohol intake do drink less while pregnant. There is no association between intention to binge drink and maternal drinking, possibly because most women find binge drinking while pregnant unacceptable.

Distant factors. A number of so-called distant factors have been found to be associated with maternal drinking. These factors are thought to influence maternal drinking through the above-mentioned determinants, but the types of mediation analyses that could confirm this were not executed in any of these studies. Maternal drinking was often - but not consistently - found to be positively associated with smoking, parity, lower rate of pregnancy planning, previous abortion, abuse, and education level. Maternal drinking was negatively associated with complications during the last pregnancy, sleep duration, being a fulltime housewife, and being married. There were no consistent associations between maternal drinking and income or employment.

Knowledge gaps

Most of these studies were not specifically designed to systematically identify all relevant determinants of maternal drinking. Moreover, not all of these studies focused on abstinence, but rather identified determinants of amounts and frequencies of drinking. Ideally, empirically identifying determinants would consist of a combination of first qualitative and then quantitative research. However, only two of the studies summarized in Table 2 have combined qualitative and quantitative research methods [118,127], and only those two studies applied a theoretical model in order to identify

determinants (i.e. the Theory of Reasoned Action and the I-Change Model). In the studies summarized in Table 2, respondents could only give answers to the questions that were asked. From our theoretical perspective described earlier, it is therefore likely that many potentially relevant determinants were not investigated. Most researchers appear to focus on knowledge and risk perception. Attitudes and perceived norms receive some attention, while self-efficacy - and especially automaticity of behaviors - get very little attention. Some studies discussed determinants such as wanting to conceal the pregnancy during the first trimester [126], or dealing with stress [130]. Very often, comparisons between pregnant women who drink alcohol and those who do not drink were not reported in these studies, even though data were available. Also, the specific findings of the qualitative pilot studies were not reported in these studies. This means that our current knowledge about determinants is very limited, and somewhat biased.

Recommendations

Target groups. The abovementioned studies are almost all about pregnant women. However, there are other important target groups [131], for instance women with unplanned pregnancies, women planning to get pregnant, and breastfeeding women. Women do not always plan to get pregnant; in fact alcohol use has been linked to sexual risk-taking and unplanned pregnancies [131]. Sedgh et al., (2014) [132] reported that 40% of all pregnancies worldwide were unintended, and that more than a quarter of all live births are a consequence of unintended pregnancies. Alcohol can disrupt fetal development at any stage of pregnancy, including the early stages before a woman knows she is pregnant [133]. Pettigrew et al. (2016) [126] compared the attitudes and intentions to reduce alcohol intake of pregnant women with possibly pregnant women and not pregnant women. The pregnant women had attitudes and intentions that were significantly different from the other groups. These findings suggest a tendency to continue drinking until pregnancy is confirmed. These other important target groups, and their environments, need to be included in future studies.

As mentioned earlier, changing maternal drinking behavior requires understanding it first. However, this is a complex issue. There seem to be some differences between earlier studies and more recent studies, as well as across countries and between cultures. Only one of the studies mentioned earlier is a Dutch study[118]. Currently, we do not have enough evidence to decide which determinants we need to target in order to promote healthy non-drinking behavior in pregnant women. We recommend that a theory- and evidence-based procedure is followed to identify the determinants of risk behaviors related to FASD.

How, then, to identify what to change in the first place? Ideally, an overview of the existing literature would be supplemented with interviews with target population

members and possibly key environmental agents (see paragraph 2.10), and the results of these two steps would be quantitatively verified so that the relative importance of determinants and beliefs can be established. Peters (2014) [111] describes this procedure as very concise and pragmatic but also carefully theory- and evidence-based, listing: 1) the basic steps for synthesizing the literature on determinants and beliefs, 2) the basic steps for qualitative exploration of determinants and beliefs, and 3) the basic steps for quantitative verification of determinants and beliefs.

2.10. Environmental Conditions

Current knowledge

It is very difficult to imagine a health promotion intervention setting that is not embedded in some kind of social or physical system (see Figure 6). The pregnant woman lives in an environment with - among others - a partner, relatives, family doctors and midwives. A child with FASD lives in an environment that includes parents, physicians, psychologists, and other health and youth care workers. The mother of a child with FASD lives in an environment alongside a child with FASD, a partner, relatives, health and youth care workers, educators, insurance administrators, etc. - and has to deal with challenges such as the extra costs involved in care, public opinion, and stigma. However, health promotion interventions often focus on individual behavior change and do not address behavior change of environmental decision makers, or agents. As outlined earlier, there are good reasons why interventions designed to prevent harm caused by alcohol exposure in pregnancy should also target these agents (see paragraph 2.13).

Environmental conditions are not likely to be under the direct control of the individual at risk for a particular health problem. They are controlled by decision-makers, external agents such as health and youth care workers, and other gatekeepers. Such external agents exist at various environmental levels: *interpersonal*, e.g. partner, child, relatives; *organizational*, e.g. health care, youth care, school; *community*, e.g. neighborhood, organizations of parents with FASD children; and *societal*, e.g. alcohol marketing, alcohol policies, costs of care [16,17,134,135].

The first step in developing an intervention for changing environmental conditions is to find out who may be in a position to make the expected change. The program planner then has to identify the desired behaviors - and their determinants - for the agent, who can actually change the environmental condition. The health promoter can then apply methods for influencing the determinants of the agent's behavior, using methods which are appropriate for changing determinants at different environmental levels. Unfortunately, almost no evidence-based information is available regarding agents, agents' behavior, and determinants thereof. The only available evidence is from stud-

ies in which pregnant women reported that their health care workers communicated that some alcohol is acceptable, instead of promoting a non-drinking norm. Some women were even told that some alcohol is good for the baby [129] or might help with the pregnancy. It has also been reported that relatives have suggested that alcohol helps, and is good for mother as well as baby [136].

Van der Wulp et al. (2013) [137] interviewed Dutch midwives, pregnant women and their partners. Pregnant women and their partners considered the midwife to be an important and reliable source of information about alcohol in pregnancy. However, the level of knowledge in pregnant women found in the study was quite low. The majority of the Dutch midwives interviewed reported that they recommended complete abstinence. Nevertheless, they did not provide pro-active advice but only gave reactive advice (i.e. they only offered advice on this topic when clients admitted alcohol consumption). Most of the interviewed midwives did not systematically screen for antenatal alcohol use and their knowledge about the mechanisms and consequences of alcohol in pregnancy was limited. The interviewed midwives largely ignored their clients' partners in any advice they provided about alcohol. Moreover, the interviewed partners were dissatisfied with the limited amount of information provided by midwives. In general, the partner's view on alcohol consumption in pregnancy was more liberal than that of their pregnant spouse, and this was an issue which they discussed with their spouse. The interview data revealed that they would appreciate having access to an objective website about alcohol in pregnancy. In particular, pregnant women consuming alcohol had received conflicting advice about alcohol from their health professionals (midwives as well as general practitioners). Apparently, not all Dutch health professionals are convinced that complete abstinence yields better pregnancy outcomes. Frequently, the recommended advice for complete abstinence is combined with remarks such as, "you can enjoy a glass of wine every now and then".

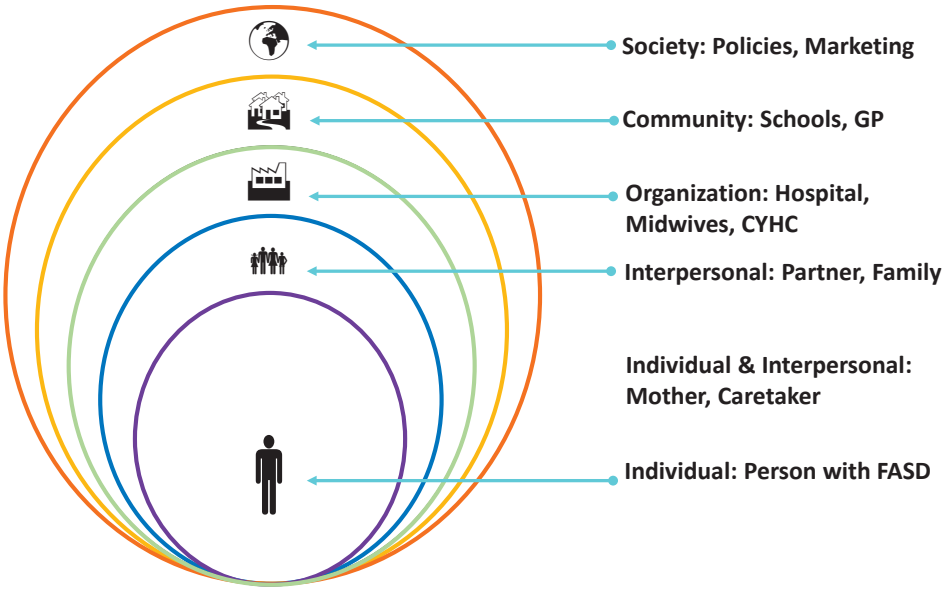

Figure 6 Environmental Conditions and Examples of Decision Makers or Stakeholders

Knowledge gaps

Who are the relevant agents in the case of FASD? The two main health promotion issues are 1) the consumption of alcohol by the pregnant women and 2) the provision of care for the mother and child with FASD. The second scenario will be described in Chapter 3: Secondary & Tertiary Prevention – Screening, early detection, management, and care.

What are the relevant environmental conditions for maternal alcohol use? To date, no systematic empirical evidence exists in relation to environmental influences on alcohol consumption by pregnant women; only incidental findings in studies on determinants: influence of the norms and behaviors of the partner and of relatives at the interpersonal level, and influence of the norms and behaviors of health care workers - especially midwives, gynecologists and obstetricians - at the organizational level. It is important to note that both sets of influences may in fact encourage rather than discourage alcohol consumption; relatives as well as professionals sometimes claim that alcohol might be good for mother and baby. In terms of environmental influences on alcohol consumption in general, there is evidence to support the influence of factors at both community and policy levels, including: drinking norms and cultures, alcohol policies, enforcement of policies, access and availability of alcohol, and marketing and pricing [e.g. ,138]. Some of these influences discourage drinking, and some promote drinking. On the other hand, there is also evidence for the role of genetics in alcohol consumption [e.g. ,139].

What are the relevant behaviors of the environmental agents? Currently, there is little available evidence. At the interpersonal level, partners and relatives of pregnant women should encourage and support the women to stop drinking and/or stop drinking themselves in the presence of a pregnant woman. At the organizational level, family doctors, midwives and other relevant health care workers should advise and help the pregnant women to stop drinking and to (among other things) deal with the stress of pregnancy in other ways than drinking alcohol. Opinion leaders in the community as well as decision-makers in policy and marketing should encourage and - if possible - enforce a non-drinking norm for pregnant women in society. Essential at all these levels, is the persistent misunderstanding that a little alcohol is acceptable; the current state of epidemiological evidence does not support this idea. The only safe guideline for pregnant women is not to drink at all.

What are the determinants of these decision-makers' behaviors? To date, no research has been carries out that addresses this question. For partners and relatives, the determinants might be comparable to the determinants that have been reported in relation to pregnant women: risk perceptions, attitudes, perceived norms, self-efficacy beliefs and automaticity of alcohol drinking behaviors. For family doctors, midwives and other relevant health care workers, the determinants might include: awareness of scientific evidence on causes for FASD, risk perceptions related to FASD, attitudes, perceived reactions of the women, (for example, worry about drinking while not knowing she was pregnant, or their estimation of the advantages of drinking e.g. stress reduction, stigma and autonomy issues), and self-efficacy beliefs related to communicating effectively with pregnant women about not-drinking. For agents at the community and policy levels, the determinants might include: acceptance of responsibility for policies regarding the promotion of a non-drinking norm for pregnant women and self-efficacy beliefs regarding the realization of such policies. Essential here is the fact that environmental levels are interdependent; agents' behaviors at one level may influence agents' behaviors at other levels. Effective policy changes promoting a non-drinking norm will facilitate behavior change of health care professionals.

Recommendations

Changing maternal drinking behavior requires understanding it first - in this case understanding the environmental influences on maternal drinking at interpersonal, organizational, community and policy levels, including the agents that are responsible for changing these environmental conditions. *We recommend that a theory- and evidence-based procedure is used to identify the environmental conditions related to maternal drinking.*

How to identify environmental conditions and agents? Personal experience, existing documents, public consultation, and interviews - starting with obvious stakeholders -

can be used to identify environmental agents, or stakeholders, and their interest in the health promotion intervention. This process continues until no new actors can be identified. Kok et al. (2015) [140] has provided a systematic description of this process, acknowledging that agents can either be supportive or unsupportive of the non-drinking message to pregnant women. When health promotors do not have enough influence on unsupportive agents, supportive stakeholders can be identified and mobilized (because of their influence on the opposing stakeholders).

The role of health care workers needs special attention. Communicating a non-drinking norm and helping pregnant women to stop drinking should be standard in health care provided to pregnant women. Promoting the implementation of good professional practices provides a rare example of an intervention targeting environmental conditions [16]. There is an existing body of knowledge on the systematic implementation and evaluation of good practices and guidelines by health care professionals [141] that can be applied to this setting.

2.11. Stigma

Current knowledge

FASD is highly stigmatized condition [142,143]. Stigmatization is the process by which a person is firstly identified as different and then devalued [144,145]. It is a process that occurs in social interactions but it is not limited to interpersonal interactions [144]. It can also take place on a broader societal level and in the intrapersonal domain. According to Pryor and Reeder [146], there are four types of stigma (see Figure 7). *Public stigma* represents people's social and psychological reactions to someone they perceive to have a stigmatized condition. It includes the cognitive, affective, and behavioral reactions of those who stigmatize, thus it entails thoughts in the form of stereotypes, emotional reactions in the form of prejudice, and behavior in the form of discriminatory actions (see also paragraph 2.11). *Self-stigma* reflects the social and psychological impact of having a stigma, and is something that occurs in those with a stigmatized condition. It includes both the anticipation of being stigmatized and the potential internalization of the negative beliefs and feelings associated with the stigmatized condition. *Stigma by association* impacts people connected with a stigmatized person and includes social and psychological reactions to being associated with a stigmatized person as well as people's reactions to being associated with a stigmatized person. Finally, *structural stigma* is stigma that is reflected, legitimized, and perpetuated by society's institutions and ideological systems. These four types of stigma are interrelated. However, public stigma is considered to be at the core of the other three types of stigma [144,146].

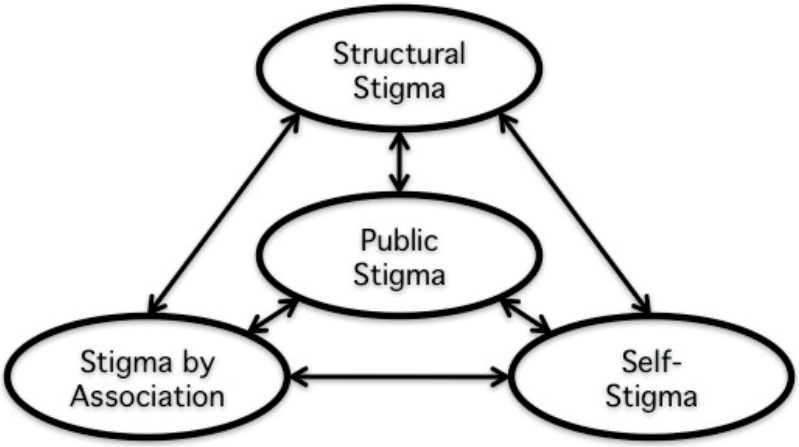

Figure 7 Types of Stigma (Based on Pryor and Reeder, 2011) [144,146]

In the context of FASD, public stigma, self-stigma, stigma by association, and structural stigma are all relevant. With regard to ***public stigma*** - the social and psychological reactions of others - the literature shows that public stigma with regard to women who use or have used alcohol during pregnancy is pervasive. FASDs are often considered to represent a women's failure as a mother [142]. Mothers are perceived as being morally culpable for a child's prenatal exposure to alcohol and ensuing FASD [142]. There is, in fact, a clear discourse of agency whereby pregnant women with problematic alcohol use are perceived to lack 'self-control' and 'voluntarily' consume alcohol in pregnancy [143]. This results in the blaming and shaming of women who use or have used alcohol during pregnancy [142,147]. The public stigma of women who use or have used alcohol during pregnancy is thus perpetuated by simplified beliefs about substance use dependence whereby people with problematic alcohol use are considered personally responsible for the onset and offset of their substance use dependence [143,148]. This predominantly moral view of substance use dependence is increasingly being replaced by biological explanations for alcohol dependence. However, research has shown that biological explanations are not a "magic bullet solution" that circumvents stigmatization. They too, albeit less intentionally, have been found to contribute to the public stigma of mothers who use alcohol during pregnancy [143,149].

It is not only mothers that are subject to stigmatization; individuals with FASD are also perceived in a negative way by society. In fact, FASD is often perceived to be indicative not only of mothers, but also of children, who apparently "place a drain on society" due to their medical and social problems (p. 68) [142]. This is in line with research showing that individuals with FASD report being misunderstood, underestimated, disrespected, bullied and blamed for the challenges they face with respect to, for example, learning [142,150]. Although individuals with FASD are not considered to be personally responsible for having acquired FASD, they are nonetheless considered

difficult and, unjustifiably, are often held responsible for their apparent inability to offset the negative consequences of FASD, such as leaning difficulties and behavioral problems [142,151]. Children with FASD are often 'othered', particularly at school. They frequently struggle to make friends and their behavior is considered to be problematic by teachers and administrators [142]. This often leads to reduced self-esteem, low self-confidence, and increased social isolation [152]. Their self-esteem and potential to succeed are further impeded by beliefs that individuals with FASD will inevitably be societal failures who are likely engage in criminal behavior and, fueled by biological explanations for substance use dependence, use drugs or alcohol [142,153].

Unfortunately, the negative beliefs and attitudes about individuals with FASD and women who use or have used alcohol during pregnancy are not limited to the domain of others (public stigma); they are also anticipated, expected, and internalized by individuals with FASD and their mothers (***self-stigma***). Research has shown that women of children with FASD engage in self-blame and hold themselves responsible for the outcome of prenatal exposure to alcohol, even in cases when they were unaware of the effects of such exposure [153,154]. In this context, mothers of children with FASD tend not to acknowledge the broader social and structural factors (e.g. poverty, poor access to treatment, other forms of marginalization) that may have contributed to their alcohol use during pregnancy, but rather focus on the personal responsibility they had and failed to take [153,155]. This self-blame has been found to impede parent-child relationships [156] and can thus decrease the problems experienced in relation to FASD. Self-stigma is also likely to occur in individuals with FASD who internalize negative beliefs about FASD, thus underestimating their own potential [157].

The stigma of FASD extends to associates of individuals with FASD and potentially also to associates of women who use or have used alcohol during pregnancy. Biological mothers of children with FASD who are primary caregivers to their child with FASD are subjected to a double burden. Not only are they stigmatized directly for having consumed alcohol in pregnancy, they are often also stigmatized as a result of their association with an individual with FASD and his or her accompanying behavioral problems or disabilities [147,155,158]. Additionally, stigma by association is felt by non-biological parents who may, as a result of FASD stigma, feel compelled to disclose that their child was adopted in order to avoid stigmatization [159].

Lastly, there is structural stigma surrounding FASD. The current literature points to three main issues that contribute to FASD-related structural stigma. The first is coercive or punitive measures that aim to reduce prenatal alcohol exposure - such as compulsory reporting of women who consume alcohol during pregnancy, removal of the parental rights of women who use alcohol during pregnancy, and criminalization of women (see also paragraph 2.12) who use alcohol during pregnancy [143]. These kinds of measures are often driven by ideological systems with strong fetus protection and

right to life movements but are highly detrimental to the reduction of FASD stigma and the prevention and identification of FASD [143]. The second major form of structural stigma is the use of public health initiatives that, in seeking to reduce prenatal alcohol exposure, promote negative judgments of alcohol use in pregnancy, and emphasize 'risk' to the child and 'responsibility' of the mother as an individual [142,143,153]. These efforts seriously undermine the provision of effective support services to women who use alcohol during pregnancy and individuals with FASD [142,143,153]. They also obscure systemic structural social inequalities and environmental conditions that contribute to prenatal alcohol exposure. It is vital that we maintain an awareness of how FASD stigma is driven and compounded by other forms of marginalization - including poverty and ethnic minority status [143].

Clearly, FASD stigma has significant consequences for individuals with FASD, women who use or have used alcohol during pregnancy, and the associates of people with FASD. We must recognize that FASD stigma is a significant impediment to the prevention of prenatal exposure to alcohol for many reasons, including the fact that stigmatization deters pregnant women with problematic alcohol use from seeking mainstream prenatal care and substance use dependence treatment [142,143,160,161]. Non-disclosure of prenatal alcohol exposure due to fear of stigmatization and penalization also inhibits the identification of FASD, which, in turn, prevents children with FASD from receiving the support they need [142]. It is thus imperative that the stigma of FASD is prioritized in both research and practice.

Knowledge gaps

Future research should investigate aspects of public stigma, self-stigma, stigma by association, and structural stigma that have not yet been fully investigated in relation to FASD.

Recommendations

Specifically, with respect to delineating public stigma and the impact and repercussions of such stigmatization, we recommend investigating beliefs held by the general population about alcohol dependence, women who use alcohol during pregnancy, and FASD. In this regard, stereotype endorsement, perceptions of agency, attitudes towards women who use alcohol in pregnancy, and endorsement of coercive policies against women who use alcohol during pregnancy are all certainly worthy of investigation. As part of this research, it may also be interesting to explore the role of gender and how views of mothers and fathers of children with FASD differ.

With regard to self-stigma, we recommend further exploring the extent to which society's negative beliefs and attitudes about FASD are anticipated and internalized by individuals with FASD and their mothers, and the ways in which stigma anticipation and

internalization impact on psychological and social well-being. Moreover, this kind of research would benefit from a delineation of the different kinds of support needed by individuals with FASD and for women who use (or have used) alcohol during pregnancy, in order to effectively promote resilience against insidious stigmatization.

Research efforts should also prioritize further investigation of stigma by association as experienced by those connected to individuals with FASD. There is a paucity of research in this regard - and it would be worthwhile to look not only at how birth mothers are affected by direct stigmatization but also at the effects of stigmatization as a result of having a child with disabilities and/or behavioral problems. Furthermore, we recommend investigating the unique experiences of fathers and of adoptive parents.

Lastly, we argue for the identification of structures that contribute to stigmatization. It is important to explore how coercive policies contribute to stigma, and it is important to identify means of structural support for the reduction of FASD stigma. Additionally, research should explore how public health prevention goals can be met without stigmatizing women who use or have used alcohol during pregnancy. Finally, there is a need for greater understanding with regard to how FASD stigma layers with other forms of marginalization that are linked to race, class, and ethnicity.

The proposed research is necessary if we are to effectively reduce FASD and FASD stigma via theory- and evidence-based interventions across interpersonal, intrapersonal, and structural domains.

2.12. Legal and Ethical Issues

Legal and ethical issues are important and complicated in relation to FASD. The updated BMA report 2016 [109] added an appendix to address this topic; Nelson and Trussler (2016) [162] addressed these issues in an edited volume entitled “Fetal Alcohol Spectrum Disorders in adults: ethical and legal perspectives”.

As FASD is an international concern, some of the relevant legal and ethical issues are considered in the following section in the abstract (i.e. not specifically limited to one jurisdiction). These issues are considered under the following four themes.

1. A typology of the legal and ethical issues in FASD first requires a consideration of **the actors involved**: the mother (biological, adoptive or foster-caregiver), the unborn child, the child born with FASD, the genetic (or social) father, broader friends and family, society in general, the medical practitioners involved, and the State (police, legal process, etc.).
2. A second axis of the legal typology comprises **areas of law**: human rights (privacy, freedom of expression, health care), child welfare and medical, tort/ delict (negligence and duty of care), criminal.

3. A third axis represents **areas of ethics**: autonomy, responsibility, solidarity, and theoretical ethics.

4. Key questions include: How relevant are legal and ethical issues in an area where there is little scientific consensus? How far should a woman's choices be limited by considerations about her unborn child (cf. abortion)? Who is responsible for the damage caused to the child through alcohol use in pregnancy? How much, in an alcohol-tolerant society, can the use of alcohol be limited in order to address FASD (to what extent are individuals - other than the biological parents - responsible for the mother and the unborn child?)?

Actors - who is at risk of harm and who might be involved in the harming?

As seen in the medical literature, there is no consensus about the cause of FASD and its wide-ranging consequences, so it is worth noting at the outset that when talking about FASD, there is no typical person involved. However, it is still worth considering the range of actors involved - the people under legal and ethical consideration when assessing harm and protection, as well as liability, in relation to FASD.

There are two primary actors in FASD - the mother and the child. From what we understand about FASD so far, **the biological mother** could be a person with high or low dependency on alcohol (although the higher the use of alcohol, particularly in the first and third trimesters, the higher the chance of FASD in the child), and she could come from a wide range of economic and educational backgrounds. If those considerations cover mothers before birth, biological mothers and adoptive or foster-caregiving mothers are also key individuals in the care of a child who has been born with FASD. **The child** needs to be considered both before and after birth. **Unborn children** are at risk of FASD if they are exposed to alcohol (although it is not clear how much or how frequent this exposure has to be to constitute a risk). What is clear is that some unborn children are exposed to a level that produces FASD. As FASD is, theoretically, completely preventable, this poses difficult social and regulatory dilemmas. **Children born with FASD** require particular welfare responses - they may have additional care needs because of their condition; meeting those needs comes at an economic cost, and often requires additional time and expertise. One crucial question is, who provides for the child with FASD? This in turn requires consideration of who is in a position to care for the child with FASD.

These dilemmas continue when one considers the broader group of actors. One approach to FASD might frame it only as a maternal responsibility problem - as far as we can see, it is only the mother's drinking that harms the child. However, drinking alcohol is a societal phenomenon. Even in cultures where drinking alcohol is outlawed and normatively unacceptable, evidence of FASD has been found. Historically, alcoholic drink was a source of reliable, safe drink; it has religious and cultural significance. Al-

cohol is, today, undoubtedly big business, with companies producing alcohol providing sponsorship of major sporting and cultural events. Many communities revolve around 'the pub', 'cafe' or 'club', and to many alcohol consumption is associated with leading a sophisticated lifestyle. To what extent, then, should the immediate friends and family of pregnant (or even sexually active) women share the responsibility for FASD-aware drinking? Certainly, there is an argument that, even though there is not (yet) an established link to the genetic father for FASD, partner support (or lack thereof) and interaction with the mother may exert an influence on the mother's alcohol consumption. How far should this be considered within the regulatory framework to prevent FASD? Even if it is not a matter for regulation, medical practitioners, social workers, the police and judiciary (as well as the mother's immediate social circle) all have a role to play in supporting both the child and the mother, and in reflecting societal norms in the treatment of the same.

Law - what is the range of Laws that relates to FASD?

We have not identified any FASD-specific laws. The laws that relate to FASD tend to focus on the welfare of the child, and civil or criminal liability for harm. Human rights, particularly the right to privacy, are relevant here. Other relevant, but less obvious laws include advertising and licensing Laws.

Human rights

Laws surrounding the welfare of the child tend, following the high expectations of the UN Declaration of the Rights of the Child (1959), to lean towards a welfare expectation. Under UK Law, for example, following the Children Acts of 1989 and 2004 [163,164], the established case law tradition of the paramountcy of the welfare of the child is established in Statute. It therefore follows that intervention decisions about the welfare of the child, for example in the face of the mother's inability to care for the child, are measured against this high, child-centered standard; the action of a welfare-providing authority must place the welfare of the child first because the welfare of the child is paramount. Thus, for a child with FASD from birth, there is a duty to consider intervention for his or her welfare (either within the context of the child staying with the mother or family, or, more drastically, by removing the child from that home environment). As with many human rights, however, this duty does not translate into a right to economic stability. There are, as the result of the right to health(care) and the Rights of the Child, claims to health and social care, but these are restricted by domestic jurisdiction economic policy limits (within the 'margin of appreciation' in international law). A child with FASD does not have an absolute right to a particular level of support, despite the seemingly robust language of human rights. However, when a child with FASD is at (severe) risk in his or her environment, there is a duty on the State to alleviate the risk.

At the same time, the right to privacy is prominent. First, under international law - the Universal Declaration of Human Rights (1948) and the European Convention of Human Rights, (1950) for example - and in domestic constitutions, the right to private life or privacy is not an absolute right; privacy is tempered by, essentially, the public interest. Conceptually, it can perhaps best be thought of as the interaction between each individual and all other individuals (acting individually and collectively), and therefore there cannot be absolute claims; privacy has to be crystallized in each situation by the negotiation of a legitimate claim on the individual's freedom of choice from others (individually or collectively). Anita Allen, the American legal philosopher, makes a useful typology of privacy in relation to genetic information that is equally useful for FASD situations [165]. Allen points to four dimensions of privacy: informational, decisional, physical and proprietary. Arguably, there is no proprietary privacy engaged in FASD, but the other three types play a role. Informational privacy - information, about the condition FASD and about the behavior leading to the condition - is covered by standard medical confidentiality, with a public interest caveat (but only a public interest caveat) allowing for the breach of that confidentiality. For example, under the Dutch WGBO, a health care professional must maintain the confidentiality of the medical records of both mother and child (WGBO, Article 7.457) [166]. Personal information related to both mother and child is also protected under data protection laws (e.g. in the EU under Data Protection Directive 95/46/EC) [167] with similar effect.

Physical privacy is covered in most jurisdictions by criminal codes and civil wrong (Torts) codes (discussed below). Decisional privacy is, conceptually, the most interesting. Decisional privacy asks - who has the right to make a decision? Allen points to the US discussion surrounding the abortion case of *Roe v. Wade* (1973) [168]. This case poses the question, 'who has the right to choose, the woman or the State?'. The privacy question is essentially the same for FASD: 'Can a woman's right to choose to drink endanger her unborn child?' It is a question that can be extended: 'Can any individual's right to choose endanger the unborn child?' As a legal question, decisional privacy balances are struck through a number of elements - through the disclosure of information, through criminal sanctions, through compensation, through welfare provisions, through education programs, through limiting access to alcohol, and the like.

Criminal law

Criminal law can operate in relation to damage to a child through FASD. Assaults against the person are covered under criminal law. However, FASD is an assault against the unborn child. These assault laws have often been part of legislation that governs against termination of pregnancy. Legal abortion is a relatively new development in the law, and is not accepted - or fully accepted - in some jurisdictions. Prior to this development, termination as a medical emergency (due to the health or life of the mother being under threat) could perhaps be accepted, but for other reasons it was

deemed unacceptable. In relation to FASD, a difficult question arises - how, in legal cultures that accept abortion, can there remain space for laws related to harming the unborn child? First, there remains a need to deter individuals from procuring abortions outside the licensed channels. In most jurisdictions, abortion is limited to a point where the unborn child would be able to survive (assisted) outside the womb (around twenty-five weeks of development). This suggests, then, that jurisdictions will accept criminal liability towards (and therefore a limited personhood of) the unborn child that is later in its gestation. Equally, many jurisdictions impose criminal sanctions for the legally improper use of embryos in research and medical science; different jurisdictions have different times at which the embryo becomes protected against research. What emerges is that the criminal rules concerning abortion, originating in a woman's right to choose, are somewhat restricted within a broader framework of limited protection afforded to the unborn child. This said, however, FASD does not sit well with the protection of the unborn child law, as was seen in a recent attempt to use such law in the UK [169].

The origin of the UK case concerned an application to the Criminal Injuries Compensation Authority. The basis of the law in question was the Offences Against the Person Act 1861, s. 23. This required both a 'guilty act' and 'guilty mind' (*mens rea*) - the intention to commit harm to the unborn child, in this case, through heavy drinking (despite warnings about the potential harm). The final outcome of the case on appeal was that the intention to harm the unborn child had not been established - a matter of fact that shows the difficulty in bringing about a charge under this type of offence. One might argue that it is unlikely that a woman will drink heavily and against warnings during pregnancy without a prior dependency on alcohol; where there is dependency, it is strongly arguable that intention is extremely difficult to prove: "I drank to harm the child", rather than "I know what it's doing to the child, but I can't stop drinking." This would, one might suggest, equally rule out criminal negligence and recklessness. This is the first difficulty in defining a criminal offence in relation to FAS and FASD. Furthermore, while medical science remains unclear as to precisely what behavior produces FAS and FASD, there is insufficient clarity to be able to define an offence of causing FAS or FASD in a child without reference to the intention of the mother. One wonders if, as a matter of public policy, there is a real desire to criminalize the relationship between the mother and the unborn child. For example, is there any public desire for other 'lifestyle' choices becoming matters of criminal liability, such as food choices, exercise choices and the like? Is there a desire to create a policed environment against women, especially where the choices are part of established generally socially acceptable behavior. Tobacco smoking is the obvious precedent here. Despite evidence of its damaging effects, general personal choice is prized over protection from any specific harm caused (by manufacturers and smokers alike). In terms of criminality, criminalizing FAS- and FASD-causing behaviors would open a Pandora's Box.

Civil wrongs - Torts or Delict

The same could be said for compensation for civil wrongs - Torts or Delict, depending on the jurisdiction. Conventional compensation is based, in many 'fault-based' jurisdictions, on the negligent behavior of one person in relation to another. Here, the mother could be shown to have a duty of care towards her child (although establishing liability to the unborn child is problematic, as discussed above), and knowingly drinking alcohol where there is a specified risk of causing FASD could, where the evidence is strong, produce a claim of negligence. However, the question remains, a claim against whom? A child suing a mother diminishes family finances by paying lawyers' fees. Even where there is personal liability insurance, the question remains whether this behavior would be excluded from the contract; practically, in cases of heavy alcohol dependence, one wonders if the premiums for personal liability insurance policy will have been maintained.

Health and welfare law

Whereas fault-based compensation for FASD may not be available for the extra health, education and general care costs of the child, jurisdictions have followed human rights commitments and provide either financial or in-kind provision for children with FASD, as they do to other children with welfare or care needs. The extent of this provision, of course, varies jurisdiction-by-jurisdiction (not least, because whereas the human rights agenda outlaws discrimination in terms of race, gender and to some extent age, it has yet to embrace discrimination on economic grounds). Welfare and health care are matters to be determined according to the politics of each country. What can be said is that whilst we have not yet found places where children with FASD are discriminated against explicitly because of the (arguably) avoidable cause of the condition, FASD children and their guardians still have to negotiate the general welfare and care landscape.

Ethics - questions and issues related to FASD

"Ethics" and "ethical" are interesting terms, as they have both a colloquial and a technical use. Colloquially, we use the terms - along with "moral" and "morality" - to indicate a sense that something is right or wrong, acceptable or unacceptable. However, these claims are not grounded in common sense or authority; they are appeals to personal beliefs about probity that individuals may or may not seek to impose upon others; they are grounded in a variety of personal or shared beliefs. There is a more technical use, however, where the claim to right and wrong is grounded in ethics theory, originating in philosophy, and this fits into a technical normative architecture of society. Here, claims to authority are more systematic, and may be based in pragmatism, belief, or claims to abstract rationality. There is, as in the colloquial use of these terms,

a struggle with relativism; claimants or theorists are more or less happy to assert an absolute authority for their ethics or morals. Thus, we have competing, contested moralities and ethics. What is clear is that there is a shared understanding that the probity of human behavior, when it impacts on others, is a matter for evaluation and, perhaps, judgement. FASD, with its (arguably) avoidable causes and extreme (if rare) effects, attracts such debate.

In this report, we do not rehearse the full range of technical ethical positions. Rather, as a general statement of the intent of ethics, we look to the four elements of Beauchamp and Childress' Bioethics [170]: beneficence, non-maleficence, justice, and autonomy. We also note the re-emergence of 'virtue ethics' in recent years, and 'discourse ethics' as creating a useful ethics architecture. Not harming and seeking to do good can, in the FASD debate, easily heap blame on the mother. However, it can be argued that there is only a very small minority of women who seek to harm their child through their own alcohol consumption. The majority, it is more reasonable to suggest, either accidentally harm their child (because, for example, the pregnancy was unknown at the early stage when the mother drank normally), or because of their dependency on alcohol - despite knowing the dangers of its consumption for the unborn child - were unable to stop drinking.

This is where ethics becomes challenging. Alcohol is paradoxical. Many cultures embrace alcohol; for many alcohol loosens social interaction; for many alcohol is 'good'. And at the same time, alcohol is medically and socially abominable. Our messages are mixed beyond belief. Our understanding of alcohol is not clear - beneficial in moderation, damaging socially and medically in excess. That confusion makes culpability extremely difficult to define, and equally, and arguably, spreads responsibility. If we want to eradicate FASD, arguably we must share the social responsibility. We must accept moderation in order to support women of child-bearing age to avoid alcohol. From university social gatherings, cafes, pubs and restaurants, to sports sponsorship deals and society in general; we must all embrace the idea that alcohol is as problematic as it is beneficial. The parallel with tobacco smoking is clear; and the social struggle with tobacco is not over.

Concepts of justice and shared responsibility are relevant to this line of argument – the idea that responsibility is more complicated than the obvious responsibility of the mother to her child, and that there is a social responsibility resulting from the confusing place that alcohol has in society. Because of the difficulty in creating the clear case about responsibility in relation to FASD, there is a broader claim for justice through socially shared responsibility; FASD requires a no-fault liability collectivism. But, in the bioethics of Beauchamp and Childress, autonomy has first claim. It is, however, only in the last 35 years that, in popular and political culture, autonomy has developed into a suggestion of absolute freedom of choice. When one looks at the philosophy of Locke,

Smith, Mill, Kant, and Kropotkin, there is arguably a shared acceptance that autonomy rests on collectivism; that free choice depends on society, and that society has certain shared responsibilities that support free individual choice. This notion has, perhaps, been lost in the predominant neoliberal economics of the last 35 years, and political interpretations of autonomy have moved away from the classic ethics moorings of individualism. In terms of FASD, especially with its (arguably) preventable cause and apparent culpability of the mother in her causal behavior, autonomy in this modern interpretation is particularly challenging. As yet, the 'sins of the mother' argument has not been a prominent one, but in an era of personalized medicine and consumer choice, the benefits of solidarity are beginning to be questioned, and the notion of the virtuous life - not as an aspiration but as a duty – becomes a foreseeable point on the horizon. These are political moral choices, and that is why we raise the importance of discourse ethics; with its acceptance that ethics are forged through careful and considered discussion, it becomes very important in democracy.

Key questions that must influence the policy discussion

There are a number of questions that arise from this short normative overview. First - what sort of society do we want to be? What is the relationship between the individual and the collective (of individuals)? Solidarity means shared responsibility - but it also requires individual responsibility. Striking this balance is not only an issue in relation to FASD; FASD is a focal point for the discussion. Children with FASD are blameless; the unborn child can be protected; the mother (apparently) has choice; those around the mother create an environment in which this choice is exercised - the responses to these claims are moral, societal choices. FASD requires resources for education and welfare programs, and which of these are funded are political choices.

A more abstract normative question related to FASD is 'where there is little scientific consensus, how far can conclusions be drawn in law and ethics?' It is clear that there are children who suffer from FASD, but the causes are not clear. There is a danger that only heavy-drinking mothers - as a most obvious target - will be blamed, when they may not be the only risk-takers. There are questions relating to proportionality and justice at one level, and effectiveness at another. FASD cannot, when the medical science is not yet clear, be narrowly defined as a problem of alcohol abuse in mothers - and by extension low-income, low-educated mothers - when the causes could be much broader.

The biggest challenge that emerges from a consideration of the normative issues relating to FASD is the social challenge that it represents. Throughout this report, the fact that the condition can be avoided has been couched in the noncommittal term "(arguably) avoidable". This is partly because of the complicated nature of the medical sci-

ence of FASD. However, it also points to the difficulty of apportioning responsibility only to the mother.

Recommendations related to ethics and law

Given the uncertainty within medical science about this topic, it would be inappropriate to criminalize women who have severe alcohol problems. Rather, the emphasis should first be on addressing the welfare of children born with FASD, second on clarifying and understanding the relevant medical science, third on educating and investing in prevention, and finally, when all these are in place, addressing issues of culpability - and in doing so placing alcohol problems within their broad social context.

Chapter 3
Secondary
&
Tertiary Prevention

3. SECONDARY & TERTIARY PREVENTION

"The diagnosis and management of the range of FASD requires a multidisciplinary approach involving a wide range of healthcare professionals – including pediatricians, obstetricians, psychologists, GPs, neurologists, psychiatrists, clinical geneticists, health visitors and midwives – as well as individuals in the fields of education and social services." (BMA, 2016, p.33 [109])

3.1. Introduction

The previous chapter described primary prevention related to prenatal alcohol exposed pregnancies. This chapter addresses secondary and tertiary prevention. Topics such as stigma and ethical and legal issues, addressed in Chapter 2, are important and need to be kept in mind for this chapter too. Secondary and tertiary prevention aims to reduce and soften the impact of FASD. The following sections will discuss diagnostic testing of FASD, neuropsychological testing, neuroimaging, pediatrics and child and youth health care, socio-economic costs, and interventions designed to promote early detection of FASD and to optimize the management and care of FASD individuals.

3.2. FASD Diagnosis

Current knowledge

Diagnostic testing. The assessment of prenatal alcohol exposure is complex. The diagnostic process is multi-faceted and requires a multidisciplinary clinical team. Hoyme et al. (2016) [182] stated "*The assessment of individuals prenatally exposed to alcohol requires a medical assessment and team leadership by a pediatrician or clinical geneticist/ dysmorphologist with expertise in the full range of human malformation syndromes and the dysmorphology evaluation of children with FASD. In addition, exposed children should have expert psychological/ neuropsychological assessment, and a skilled interviewer should evaluate prenatal maternal alcohol intake. Other team members may include developmental behavioral pediatricians, psychiatrists, speech pathologists, occupational therapists, physical therapists, special educators, audiologists, and/or ophthalmologists.*"

There is much discussion about which diagnostic criteria to use. Different tools for assessing FASD have been developed and several initiatives have been undertaken to achieve consensus on the most useful FASD criteria and diagnostic processes. Commonly used guidelines are:

- IOM criteria (Institute of Medicine United States).

Stratton et al., (1996) [183] described five diagnostic categories recommended by an expert panel of the Institute of Medicine in the United States: (1) fetal alcohol syndrome with confirmed prenatal alcohol exposure; (2) fetal alcohol syndrome without confirmed prenatal alcohol exposure; (3) partial fetal alcohol syndrome with confirmed prenatal alcohol exposure; (4) alcohol-related birth defects; and (5) alcohol-related neurodevelopmental disorder. These categories, however, lack a specified set of parameters (e.g., exact facial dysmorphic features, specific cognitive characteristics). In 2005, the IOM published revised diagnostic criteria to provide further clarification of the guidelines proposed in 1996 [184].

- 4-Digit Diagnostic Code

A 4-Digit Diagnostic Code was developed by Astley and Clarren (2000) [185] and Astley (2013) [186]. This tool takes into consideration the four key diagnostic features of fetal alcohol syndrome: (1) growth deficiency; (2) the characteristics of facial phenotype; (3) central nervous damage/ dysfunction; and (4) gestational alcohol consumption.
Astley and Clarren developed this new diagnostic code to provide a more objective, quantitative scale to measure and report key parameters of FASD diagnosis.

- Canadian guidelines

In 2005, Chudley et al. [187] published the Canadian guidelines for FASD diagnosis. Cook et al. updated these guidelines in 2016 [188]. These Canadian guidelines are considered to be golden middle way between IOM and 4-Digit guidelines.

The various guidelines provided for diagnostic testing and their subsequent refinement illustrates the complexity of the topic. Riley, Infante, and Warren (2011) [189], and recently Hoyme et al. (2016) [182] and Coles et al. (2016) [190], made a comparison of the existing guidelines. Agreement on a universal diagnostic system for FASD has yet to be reached. Hoyme et al. (2016) published an FASD diagnostic algorithm incorporating the updated clinical diagnostic guidelines for diagnosing FASD which provide more clarity and specificity for the accurate diagnosis of infants and children prenatally exposed to alcohol [182].

FASD data of a Dutch outpatient clinic have been published by Swelheim et al. (2014) [89]. The applied diagnostic system was based on the 4-Digit Diagnostic Code and the multidisciplinary team included a pediatrician, child psychiatrist and child psychologists.

Knowledge gaps

Different FASD diagnostic criteria (e.g., IOM, 4-Digit, Canadian guidelines) are used internationally [9,14,183,185,187,188,191]. Consensus on FASD diagnostic terminology has not yet been reached. Significant progress has been made in clarifying and operationalizing criteria.

Recommendations

Establishing a diagnosis within the spectrum of FASD is not easy, not least because of the lack of clear biological markers and reliable measures of prenatal alcohol exposure. Moreover, the consideration of differential diagnosis is important. It is essential to exclude related conditions before a diagnosis of FASD can be made. In order to make an accurate FASD diagnosis, a multidisciplinary assessment is important. Experienced gynecologists, clinical geneticists, pediatricians, psychiatrists, and psychologists should be part of the team responsible for making the diagnosis. A standardized international approach for the diagnosis of FASD and the application of a uniform diagnostic algorithm should be a priority for the Netherlands.

3.3. Neuropsychological Testing

Current knowledge

Prenatal exposure to alcohol and neurobehavioral functions. Prenatal exposure to alcohol has been associated with lifelong impairments in emotions, behavior regulation, social interactions, and cognition. For example, numerous studies have shown that individuals prenatally exposed to alcohol have an increased risk for developing externalizing problems such as oppositional defiant disorders, conduct disorders, and attention-deficit/hyperactivity disorder (ADHD), as well as internalizing problems such as anxiety and major depressive disorder [192–194]. These so-called neurobehavioral functions may be 'more sensitive' to prenatal exposure to alcohol than e.g., physical features of an individual, such as facial characteristics and physical growth, since neurobehavioral impairments (such as cognitive impairments) are observed in both children prenatally exposed to alcohol with and without physical dysmorphology [195,196]. In the following sections, the effects of prenatal exposure to alcohol on cognitive functioning will be discussed in more detail.

Alcohol exposure and intelligence. Research has repeatedly shown that prenatal exposure to alcohol may lead to lower scores on test batteries measuring intelligence in (young) children, adolescents, and adults [197,198]. Wechsler (1938) [199] defined 'intelligence' as "the *global* capacity of an individual to understand the world around him and his resourcefulness to cope with its challenges". In line with this, many researchers have shown that intelligence estimates are an early and robust predictor of important life outcomes, such as academic performance, college readiness, and social interactions, in both standardization samples and clinical populations [200,201]. Although test batteries vary in how they operationalize intelligence, intelligence estimates (often referred to as 'full scale IQ' or FSIQ) are, in most test batteries, based on the summation of 'points earned' across multiple subtest(s) measuring one or more cognitive functions, with each subtest being accorded the same weight as the other(s)

[202]. Typically, reports on FSIQ scores in individuals prenatally exposed to alcohol range from low average to borderline (i.e., ≥ 1-2 standard deviations (SD) below the mean). However, not all of these individuals display low(er) FSIQ scores [195].

It is tempting to conclude that FSIQ scores based on different test batteries 'capture' the same global capacity to understand one's environment and to cope with its challenges. However, intelligence test batteries vary in terms of the subtests mentioned above and therefore also in the diversity of cognitive functions tapped by the test batteries. The correlations between scores on different cognitive subtests are far from perfect. Therefore, administering diverse test batteries claiming to measure intelligence to one person may lead to different FSIQ scores, depending on the match between the specific cognitive functions that are tapped by the test battery and the specific strengths and weaknesses in the profile of cognitive abilities of that individual [203]. One could question the validity of FSIQ scores in the presence of significant variability in subtest scores within an individual. However, Watkins, Glutting, and Lei (2007) [204] have shown that FSIQ is an equally valid predictor of e.g., school success in a group of individuals that showed significant within-subject variability among subtest scores and a group that did not show such variability. Nonetheless, the identification of an individual's cognitive strengths and weaknesses (i.e., in terms of the specific cognitive subtest scores) is more likely to provide professionals with a clear direction regarding a plan of action (or treatment) than an FSIQ score. For instance, some children may have attention problems explaining why they cannot cope with their environment, while others may have intact attentional functions but problematic planning skills. It is likely that these problems will need to be addressed differently. It is therefore important to study *specific* cognitive functions in this context.

Alcohol exposure and specific cognitive functions. According to Anderson (2002) [205], it is important to test at least four distinct, but interrelated, clusters of cognitive functions when studying how well someone copes with the challenges of daily life - he called these 'executive functions': i.e., (1) attentional control, selective attention, and inhibition, (2) cognitive flexibility, divided attention, and working memory, (3) goal setting, planning, and reasoning, and (4) information processing, including fluency and speed of processing. These clusters are believed to 'build on one another' and are thought to be regulated by neural networks including the (dorsolateral) prefrontal cortex (PFC), the basal ganglia, and the thalamus [206,207].

Ware and colleagues (2015) [208] have found that prenatal alcohol exposure is associated with both volumetric and functional changes in these neural networks. In line with this, for each cluster, numerous studies have revealed, on average, lower scores on tests measuring these clusters in individuals who are prenatally exposed to alcohol, compared to individuals born to mothers who did not use alcohol during pregnancy (e.g., [209–211]). Not only these so-called executive functions may be influenced by

prenatal alcohol exposure: impairments in learning, fine-motor control, auditory processing, language delays and disorders, visuospatial weaknesses, and academic skills such as mathematical comprehension, reading and spelling, have repeatedly been reported in this context [212–214]. In sum, prenatal alcohol exposure seems to be associated with multiple cognitive and academic problems. Anderson (2002) [205], stated that professionals must always identify "the nature of a cognitive deficit (e.g., knowledge, performance, fluency) in this context. Students with knowledge deficits do not have the information or skill in their repertoire or do not know how to use a skill in a particular situation. Students with performance deficits have the knowledge and skills, but they fail to use them at acceptable levels. Fluency deficits are the result of insufficient exposure to models of the behaviors, insufficient opportunities to practice the behaviors, or inconsistent reinforcement of their performance of the behaviors".

It is worth noting, however, that the cognitive impairments reported in this overview have also been documented for groups of individuals with developmental disorders, such as attention-deficit/hyperactivity disorder (ADHD), autism, and learning disabilities [215–217], but also in typically developing children [202,218]. As stated by Watson, Westby, & Gable (2007) [219], it is essential "to recognize the characteristics of cognitive dysfunction, regardless of its cause, if students are to receive appropriate interventions". Also, the studies discussed above report on group averages: this may mean that there are individuals prenatally exposed to alcohol who do not display any of these cognitive difficulties. Therefore, professionals should not assume that each individual prenatally exposed to alcohol will show cognitive difficulties (either global or specific).

Triple pathway model to study neuropsychological heterogeneity. Traditionally, cognitive functions are examined using so-called 'cool' cognitive tests, i.e., by administering "abstract, decontextualized problems that lack a significant affective or motivational component" [220]. However, Sonuga-Barke and colleagues (2010) [207]postulated in their triple pathway model that - in order to predict how well an individual understands the world around him (or her) and can cope in it - one should not only study these 'cool' cognitive functions, but also the influence of motivation (or as they also call it reward processing, signaling of delayed rewards, and delay aversion) and temporal processing (also called timing). To illustrate this, think about a child who has recently failed his geometry exam. Many factors could have contributed to this end result: the child may not have known how to prepare for the test, or may have difficulties with visuospatial reasoning. These are cognitive explanations. However, there are alternative explanations; he child might have sufficient cognitive abilities but have underestimated the time needed to prepare for the test sufficiently (i.e., a time perception problem) and/or he might have lacked the motivation - or not received enough immediate reward - to prepare for it, and therefore did not spend enough time studying.

Neuroimaging studies have validated the claim that different (though partly overlapping and interdependent) neural networks underlie these three components. To provide an example, motivation and reward processing seem to be regulated by neural networks including the (ventrolateral, orbito) PFC, the basal ganglia, and the thalamus, whereas the cerebellum, basal ganglia, and the PFC seem to regulate temporal processing [207]. In line with this, research has shown, for instance, that damage to the orbito PFC can lead to normal performances on tests measuring 'cool' cognitive functions, but to abnormal performances on tests measuring motivation, such as the Iowa Gambling Task, or to reports of problems in daily living [221,222]. In everyday life, (cognitive) decision making is rarely conducted in the absence of e.g., motivational influences and temporal processing. This might explain the inconsistencies often observed between performances on traditional measures, testing primarily 'cool' cognitive functions, and real life behavior [205].

The number of studies investigating motivation and/or temporal processing, and the neural networks underlying these components, in individuals prenatally exposed to alcohol is highly limited - especially in comparison to the large amount of studies investigating effects of prenatal alcohol exposure on 'cool' cognitive functions. Nevertheless, these studies provide support for the notion that prenatal exposure to alcohol can indeed influence both motivation and reward processing [209,223], and temporal processing or timing [224], and that these alcohol-related findings are not fully explained by impairments in 'cool' cognitive functions [209].

Although these three components - cognition, motivation, and temporal processing - are interrelated, they represent unique and independent neuropsychological functions and, as a consequence, can be uniquely impaired in individuals. It is highly likely that studying these distinct domains will reveal a neuropsychological heterogeneity among individuals prenatally exposed to alcohol, although this claim has not yet been investigated to the best of our knowledge. However, Sonuga-Barke showed that a substantial subgroup of individuals with ADHD, a developmental disorder often diagnosed in children prenatally exposed to alcohol [225], are affected in only one domain (i.e., 6.4% of the individuals were affected only in terms of 'cool' cognitions, 19.5% only in terms of motivation, and 24.7% only in terms of temporal processing). It is important, therefore, that when studying the neuropsychological profile of children prenatally exposed to alcohol, all three components are tested separately. As mentioned before, the identification of an individual's strengths and weaknesses in the neuropsychological profile (i.e., on these three components) can provide professionals with a clear direction regarding a plan of action (or treatment). Remember the child who did not pass his geometry exam.

Knowledge gaps

Future research should investigate tests measuring cognition, motivation, and/or temporal processing. Moreover, research should focus on the validity of these tests (in relation to FASD) in a developmental context, and norm data should be collected for representative standardization samples.

Recommendations

In order to plan and develop specific individual- interventions that are aligned with diverse needs (for instance in a school environment), it is essential that professionals are able to accurately assess these individual strengths and weaknesses (e.g., as related to cognition, motivation, and temporal processing). Care should be taken to select tests that are appropriate for testing a specific person and that are psychometrically sound (i.e., reliable and valid) [195,226]. Unfortunately, the list of possible neuropsychological tests measuring cognition, motivation, and/or temporal processing is somewhat limited. Tests measuring the latter two components are still scarce, and often only available in a research context. Moreover, many of the tests available were originally designed to study adult performance. Adult-derived tests may tap into other skills in children [205], therefore the validity of using these tests in a developmental context needs to be established. Furthermore, norm data collected for representative standardization samples are often lacking. There are several factors that should be taken into consideration when collecting norm data, for example: the number of individuals included in standardization samples should be large enough, the samples should be representative (e.g., of age, sex, school type, degree of urbanization or percentage of immigrants, level of parental education), and the individuals should be randomly recruited, since these factors are likely to influence neuropsychological test performances [226]. Importantly, these tests need to be validated and norm data need to be collected for specific developmental stages, in order to provide optimal care to individuals prenatally exposed to alcohol.

An additional problem in this field is that the reliability coefficients of these neuropsychological tests (independent of what they are measuring) are often low to moderate. This leads to (fairly) large margins of measurement error, even for tests with reliability coefficients of above 0.90, which are qualified by most test reviewing committees as 'good' [226]. The findings of Van Boxtel & Hemker (2009) [227] illustrate this point. They studied the effects of measurement errors related to a specific Dutch Intelligence Test for school-aged children, that has a high reliability of about 0.95 (depending on the IQ index score used). FSIQ scores on this test have an average of 100 points and a SD of 15 points. The authors found that this reliability coefficient leads to a 90% confidence interval of plus or minus 6.61 FSIQ points. So, one knows with 90% certainty that the observed FSIQ score for an individual on this test will fall within a range of 13

IQ points on any given day. This means, for example, that when an individual's FSIQ score is recorded as 86 on day 1, another administration of the test will likely lead to a FSIQ score falling between 79.4 (which is interpreted as a borderline to moderate impairment) and 92.6 (interpreted as an average score) on day 2. This is not unique to this specific test, but typical for any test with similarly high reliability. The problem becomes greater when a test with lower reliability is used. Unfortunately, the reliability coefficients of many neuropsychological tests are in fact lower.

Furthermore, the main outcome measure of the majority of traditional neuropsychological tests is an overall performance score (e.g., the number of correct responses over time). However, these neuropsychological tests mostly tap into a variety of both executive functions and non-executive functions. Therefore, this overall outcome measure does not provide information about the specific mechanisms underlying poor test performance. To overcome this limitation, Anderson (2002) [205], for one, suggested that test performance should be analyzed using "a micro-analytic approach that incorporates quantitative (e.g., latency, number of errors etc.), qualitative (e.g., motivation, distractions) and cognitive process (e.g., strategies, actions) methodologies". Scoring systems that are devised to register as much (specific) information about test performance and normative data as possible, in order to compare these (sub)scores to those of other individuals, are likely to enhance the diagnostic utility of neuropsychological tests. It should also be noted that traditional tests provide little understanding of the child's potential to learn after obtaining instruction [228]. Multiple factors - such as the amount of education, practice with testing, and parental support - influence test performance. Dynamic testing paradigms seem to be a promising method that can be used to quantify "the learning potential of the child during the acquisition of new cognitive operations" [229]. Here, children continuously receive feedback on how they perform, while the tasks administered become increasingly difficult or challenging for the child. The idea is that "with graduated prompting and trial-by-trial-assessment this method could reveal the development of children's strategy use while tested" [230]. Modern technology provides the opportunity to construct dynamic test protocols that can be used to quantify learning potential and progress in individuals prenatally exposed to alcohol.

Researchers such as D'Onofrio and colleagues (2007) [231] have indicated that it is necessary to investigate factors which may confound the results in studies associating neurobehavioral impairments with prenatal exposure to alcohol, for example: exposure to multiple drugs, the timing of drinking alcohol during pregnancy, family-related factors (e.g., family conflict), parental characteristics (e.g., parenting styles, parental cognitive abilities, and income), and the level of alcohol exposure. To illustrate this point, a dose-response relationship between the amount of maternal alcohol consumed and the severity of the children's neurobehavioral impairment (e.g., in terms of cognitive functions) has been identified repeatedly, although maternal alcohol con-

sumption even at low levels has already been shown to be adversely related to neurobehavior [232,233]. These potentially confounding factors may also have influenced the results discussed above on the association of prenatal exposure to alcohol and cognition.

Finally, it should be stressed that the proper diagnosis of a child's strengths and weaknesses is not limited to the collection of test data and observations alone. It is essential to interpret these test data in the context of e.g., age, developmental stage, and the psycho-social environment of the individual. Diagnosing an individual's strengths and weaknesses is just the starting point. Finding an explanation for the problems should lead to one or more appropriate recommendations or interventions. The first step in addressing problems is to inform and educate the individual and the individual's environment (e.g., partner, parents, a child, a teacher or a boss), i.e., psychoeducation. Here, professionals need to realize that an individual has often received earlier diagnoses to explain their behavior - and that a new diagnosis should be integrated into existing beliefs about what is going on with the individual. The professional care giver needs to discuss the expectations of the individual and/or the environment and, if necessary, help to adjust these expectations in relation to the findings of the psychodiagnostic assessment. In addition to psychoeducation, the professional can, based on the analysis of the individual's strengths and weaknesses, opt for a range of additional (cognitive) behavioral techniques and/or pharmacological therapies [234]. Ideally, these interventions should be carried out systematically, intensively, and aligned with the specific needs of the individual, in order to produce positive results [235]. Again, remember the child who did not pass his geometry exam: if the child does not understand the content of the materials that he had to study, he will need a different kind of guidance to, for example, a motivated child who doesn't have a realistic view on how much preparation time it takes to pass the exam and does not know when to start studying in time. Within the group of individuals prenatally exposed to alcohol, these needs can be heterogeneous and can vary per person, as explained earlier. Unfortunately, studies evaluating the effects of neuropsychological interventions are still inconclusive, and only very few studies have investigated their effectiveness and efficacy in individuals prenatally exposed to alcohol [209,236]. The majority of research on neuropsychological interventions has been conducted in healthy individuals (children, adults) and/or children with learning disabilities, such as ADHD, without taking the heterogeneity of these populations into consideration (i.e., a 'one-size-fits-all' approach). Moreover, research on neuropsychological interventions has often focused only on improving specific 'cool' cognitive functions, such as working memory. In general, these studies have shown that, by repeating a task (e.g., a working memory task), individuals become better in performing that task (i.e., near transfer effects), and they often also perform better on tasks that resemble the task practiced (for instance on other working memory tasks; i.e., intermediate transfer). However, in most cases, this

practice does not seem to transfer to improvements on tasks measuring other cognitive functions (e.g., nonverbal reasoning tasks; i.e., far transfer). Interestingly, although the majority of these studies did not find far transfer effects, some studies did. Researchers need to further investigate what causes these far transfer effects, such as changes in motivation or a strategically different use of cognitive resources [237], so that they can optimally assist individuals in need.

3.4. Neuroimaging

Current knowledge

Since many of the symptoms of FASD relate to behavioral and cognitive differences, great interest has been shown in how these symptoms may correlate to changes in the brain itself. This may involve changes in function, changes in structure, or both. Various techniques exist for examining the brain, which can be grouped together under the term 'neuroimaging'. The application of neuroimaging to FASD has been summarized in several good reviews of the literature [238–240].

In terms of examining brain *activation*, several techniques are available and have been applied to this area of research, particularly MEG, PET, SPECT, and MRI, each with their own benefits and restrictions. MEG – magnetoencephalography – uses sensitive sensors to detect the tiny changes in magnetic field caused by neuronal currents when a piece of cortex is active. MEG has a very good time resolution but suffers from poorer spatial resolution. PET – positron emission tomography – and SPECT – single photon emission computed tomography – instead use radioactive tracers (such as flouridioxyglucose) whose concentration in tissue is related to some physical parameter (e.g. the metabolism of glucose). PET and SPECT tend to have poorer time and spatial resolution, but the results can be accurately related to physiological parameters. A disadvantage of these techniques is that the necessity of administering radioactive tracers means that these methods are considered to be rather invasive.

Many studies have instead used MRI – magnetic resonance imaging. MRI uses the magnetic resonance phenomenon to detect molecules containing hydrogen - predominantly in water - and create images of the subject. Various methods are available within MRI to collect different kinds of information from the tissue being examined. Most simply, an image of the structure of the brain can be made with good resolution (submillimeter in some cases) to look at the overall structure and morphology of the tissue. It is also possible to sensitize the acquisition to the direction of the diffusion of water within the tissue. By making multiple acquisitions while changing the sensitizing direction and then performing a tensor analysis, it is possible to determine the predominant direction of the water diffusion, a technique referred to as diffusion tensor imaging (DTI). FASD studies that have used DTI have mostly examined two derived

parameters, the fractional anisotropy FA (i.e. a measure of how non-isotropic the diffusion of water is, which is thought to correspond to how organized and structured the tissue is) and the mean diffusivity (i.e. how far the water can diffuse, which is believed to correspond to how restricted the water is and therefore how organized the tissue is). DTI studies of FASD subjects have shown significant differences between FASD subjects and controls, suggesting that cortical networks may be altered (for a review of DTI in see [241]).

Additionally, MRI can be used to look at brain function – functional MRI or fMRI – through an effect known as BOLD – blood oxygen level dependent contrast. This occurs due to the fact that oxy- and deoxyhemoglobin have different magnetic properties, and so a change in oxygenation level can cause a small change in the MRI image intensity. By acquiring a time series of images while e.g., presenting visual stimuli and then analyzing this time course for these small changes, it is possible to detect where blood flow has changed, and this is then related to brain activation. While this method is indirect and with a coarser time resolution than MEG, the spatial resolution is excellent, and there is no requirement for tracer injections as with PET and SPECT.

In terms of brain morphology, many neuroimaging studies of FASD have shown a correlation between prenatal alcohol exposure and reduced total brain size. These reductions are not necessarily uniform, and some studies which corrected for overall brain size reported that size variations were still observable in specific brain areas, even in subjects with no facial dysmorphia. Changes in brain shape (e.g., cortical folding) have also been observed, with particular effects in the corpus callosum.

Functional brain studies, particularly fMRI studies, have examined both the level and the pattern of brain activity during cognitive tasks as well as measuring functional connectivity between cortical areas. Of note here is that differences have been observed in which areas are activated in the brain when the same task is performed by subjects and controls, implying that different cognitive strategies are being used.

Knowledge gaps

Despite the fast-growing field of MRI, researchers have not yet been able to measure the direct impact of prenatal alcohol exposure on the brain. Further research is needed to understand brain morphology and functional connectivity between cortical areas.

Recommendations

The observed changes - in both structure and function within the brains of individuals with FASD - are of great potential value for both understanding the cognitive deficits exhibited, as well as for improving future treatments. The knowledge that individuals with FASD likely employ different cognitive strategies may imply the need for different

therapy approaches to build on the cognitive strategies that individuals with FASD are already using.

It is worth bearing in mind that MRI is in itself a fast-growing field, with new and improved techniques being rapidly developed. These have the potential to enhance our knowledge and deepen our understanding of FASD. For instance, while studies have so far concentrated on FA and MD, diffusion MRI may be able to deliver much more detailed information about tissue structure. Examples include the developments in higher spatial and directional resolution for DTI in initiatives such as the Connectome study (which help reduce confounding effects such as crossing fiber tracts), as well as the development of methods used to extract information such as axonal diameters. These may contribute to a much better understanding of the effect of PEA on the exact structure and connectivity of the brain. Another example is the improved spatial and temporal resolution of fMRI with Simultaneous MultiSlice (SMS) techniques, which can lead to improved detail of the differences in cortical connections and activation areas. A better understanding of these different networks, their differences in construction, and differences in cognitive processes, may contribute towards improved therapy for individuals with FASD.

3.5. Child and Youth Health Care

Lifespan is one of the important dimensions around which the Dutch health care system is organized. In the following sections, the management and care provided for infants, children, adolescents, and adults from the perspective of the stakeholders - pediatricians and child and youth health care professionals - will be described. For maternity care see paragraph 2.6.

Current knowledge in pediatrics

In the Netherlands, an existing national perinatal database collects data on most pregnancies and neonates, including all academic patients (see paragraph 2.6). Registration of FAS in this database is almost non-existent, pointing to a severe problem of under-registration (or under-diagnosis). The Dutch Pediatric Center collects data on specified disorders over several years (Nederlands Signaleringscentrum Kindergeneeskunde), and collected data on FAS in 2007 and 2008 [242]. In total, data on only 56 children were gathered, mainly from adopted children or children under custody, pointing to an enormous selection bias. Using questionnaires, only 39 of the 56 were confirmed to have FASD [243].

Pediatricians and pediatric health care workers are regularly confronted by alcohol problems in adolescents. Pediatric multidisciplinary alcohol clinics may have a preventative effect on later pregnancy-related alcohol consumption and possibly contribute

to the prevention of FASD in this high-risk group. However, pediatricians and pediatric health care workers are less familiar with FASD itself. As syndromes in the spectrum of FASD are not easy to diagnose and FASD has a wide differential diagnosis, it is important to be alert to the possibility of FASD and to have a thorough and up-to-date knowledge of the diagnostic criteria (see paragraph 3.2). Reasons for missing the diagnosis include insufficient knowledge and time constraints - but also fear of stigmatization (see paragraph 2.11).

Knowledge gaps in pediatrics

There is a need for better registration of FASD problems in the field of pediatrics. There are currently no guidelines for interventions once the diagnosis of syndromes in the FASD spectrum has been established.

There is a lack of knowledge about (bio)markers which can assist in the diagnosis of FAS (see paragraph 2.4). New MRI techniques, biochemical biomarkers of damage or development in the brain or other organs (e.g., liver), biomarkers of alcohol products (e.g., in meconium), and many other developments have not been explored to their full potential in relation to FAS. In summary, more research is needed.

Recommendations for pediatric care

More emphasis placed on FASD and a better structural education (e.g., recognition, diagnostic approaches, management and care) for all caregivers in pediatric care is clearly needed. This should start in basic professional education (for doctors at MD bachelor and Masters level), and it is especially important that this should continue during specialist training (for pediatricians, geneticists, and child neurologists, to specify all potential members of a FASD multidisciplinary team), and in post-graduate training courses. Paying particular attention to FAS within the pediatric training syllabus (covering themes that must be learned) would be a good start. Also, translation of existing guidelines into national and local protocols is necessary (in hospitals but also in the public health field).

Accurately diagnosing individuals within the spectrum of FASD is of great clinical importance, given the high rates of missed diagnosis and misdiagnosis. Good examples of decision trees for identifying children affected by prenatal alcohol exposure within pediatric care are available and should be used [244].

In conclusion, recognition of FASD needs to be improved, and more attention should be paid to education, intervention implementation and research. More research is also required to further our basic knowledge on (bio)markers that can help diagnosis of FASD.

Current knowledge in child and youth health care (CYHC)

Prevention, early recognition and timely identification of FASD cases are necessary - first to reduce the adverse effects of FASD and second because affected children need long-term support [245,246].

In 2005, the Dutch Health Council published an advisory report on the risks of alcohol consumption as related to conception, pregnancy and breastfeeding [247] (see paragraph 2.6). However, this report did not at any point address the potential contribution of the child and youth health care system in reducing morbidity related to FASD. This is noteworthy because the Netherlands has established a high quality system of preventive child and youth health care based on a unique standardized child and youth health program underpinned by legislation (Public Health Act) [38].

Preventive child and youth health care (CYHC) in the Netherlands (in Dutch: *jeugdgezondheidszorg, JGZ 0-18*) provides preventive care for all children aged 0 to 18 years. Until the age of 4, children visit child health centers (in Dutch: *consultatiebureaus, JGZ 0-4*) for health check-ups. The child health centers also provide medical and parenting advice. The most important aspects of preventive child health care are monitoring of growth and development, early detection of health problems (or risks) or social problems, screening and vaccination, and providing advice and information concerning health and development. This care is provided by specialized physicians and nurses. The child health care centers have a high coverage: almost all children have more than one appointment in their first year of life. Before their fourth birthday, children have visited a child health center on average about 15 times. After the child's fourth birthday, preventive child health care is taken over by the Youth Health Care Division of community health services (in Dutch: *GGD*) for children and adolescents aged 4-18 years. Specialized physicians and school nurses offer routine health checks to all children at the ages of 5, 10, 13 and 16 years, free of charge, in addition to health and developmental assessments and anticipatory guidance for children at risk. They work together with other healthcare professionals, schools and welfare services. At each appointment, specialized physicians and school nurses look at the specific circumstances of the juvenile and their family. If needed, additional appointments can be arranged; for example, home visits and other evidence-based interventions are available. Challenges for professionals working in child and youth health care include both the prevention and early detection of FASD.

Challenges for CYHC in the field of prevention:

Prior to pregnancy, preventive interventions may focus on contraception, pregnancy planning, and awareness of FASD [248].

The complex issues surrounding FASD challenges CYHC professionals to contribute to preventive interventions:

- by stimulating health education at secondary schools to increase awareness about the importance of primary prevention of alcohol-exposed pregnancies;
- by focusing on non-pregnant adolescent women with risk factors (substance abuse, mental ill-health, low SES, women having already given birth to a child diagnosed with FASD, women born to biological parents with a history of alcohol abuse, women fostered/adopted during their childhood) [182];
- by offering at-risk adolescents anticipatory guidance, helping adolescents develop the skills to make responsible decisions and healthy choices (in terms of preventing unintended pregnancies), and advising adolescents, prior to conception, about the risks of alcohol use during pregnancy and about FASD;
- by focusing on any subsequent pregnancies of a mother with a child with FASD: whenever a child receives an FASD diagnosis, an opportunity arises for discussing FASD prevention for any future pregnancies.

Knowledge gaps in child and youth health care

Many children with FASD remain undiagnosed because there is a lack of accurate, routine screening in preventive child and youth health care. Thus, present prevalence rates of FASD underestimate the extent of these disorders: documentation on intrauterine alcohol exposure is inconsistent and registration of early symptoms characteristic of prenatal alcohol exposure is incoherent. Assuming that pregnant women do not drink alcohol is unjustified. Reassuring pregnant women with information “that a glass of wine occasionally is no problem” is incorrect and should be regarded as bad practice. Greater awareness and consistent screening are needed to be effective in identifying early symptoms and signs included under the FASD umbrella. Early and timely identification of FASD-suggestive dysmorphic features and associated problems is exactly what should occur during well-child visits to the health centers. Greater awareness and consistent screening are needed in order to be effective in identifying and diagnosing FASD [182].

Recommendations for child and youth health care

Professionals involved in child and youth health care should bear FASD in mind when evaluating children with developmental problems, behavioral concerns, or school failure. This is particularly relevant for children in foster care, especially if drug or alcohol use by a parent was a contributing factor to the child being placed in care. Like other children with complex medical or behavioral disabilities, children with FASD need special attention in terms of the provision and coordination of care, and to ensure that the necessary medical, behavioral, social, and educational services are provided. Early diagnosis of FASD has a protective effect; children who are not diagnosed experience higher rates of secondary problems, including disrupted education, delinquency, insti-

tutional confinement, inappropriate sexual behaviors, and alcohol/drug problems [245]. Finally, certain sociodemographic factors should trigger an assessment for an FASD, such as foster care, international adoption, or belonging to known risk groups [249].

Professionals working in child and youth care have a basic task in public health for children and adolescents [250], so they should not evade their responsibilities in terms of the spectrum of FASD prevention approaches available. It is important for professionals working in child and youth health care to encourage cooperation between disciplines in order to tackle both alcohol consumption during pregnancy and FASD-related problems.

3.6. Socio-economic Costs

Current knowledge

The high prevalence of FASD produces an immense burden on society in financial terms, unrealized productivity, and human suffering. In the United States, annual cost estimates have ranged from $74.6 million in 1984 to $4.0 billion in 1998. In 2007, the estimated annual cost of FASD in Canada was CAD $5.3 billion [14].

Little is known about the societal costs of FASD. One systematic review of studies concerning the economic impact showed that the literature on this subject is scarce, and that the evidence is limited to North America, i.e. Canada, and USA [21]. An update carried out for this knowledge synthesis revealed additional studies on this topic - one from Canada relating to different aspects of FASD [251–259], and another study from Sweden [260]. This limited number of studies looking at the societal costs of FASD do, however, show comparable results - that is, that the costs of FASD are relatively high - for the individual, the family, and for society. Moreover, these studies show that the costs of FASD are not only related to the healthcare sector but that the majority of the costs are borne by other sectors, for examples, costs due to (special) education, productivity losses, and law enforcement.

To our current knowledge, there are only three economic evaluation studies [261–263] which look at the cost-effectiveness of interventions for FASD based on a model. A study by Hopkins et. al., (2008) [261] compared universal screening versus targeted screening for fetal alcohol exposure. This study examined the cost-effectiveness of testing meconium to detect fetal alcohol spectrum disorder in newborns. From a societal perspective, screening and treatment was economically attractive if it was implemented universally, and was a dominant strategy if it was targeted to those at high risk. Another study by Thanh and colleagues (2015) [263] looked at the cost-effectiveness of a parent-child assistance program for preventing FASD. The results of this study indicate that implementing a parent-child assistance program can also be

cost-effective. Finally, Popova et al. (2013) [254] proposed that the use of specialized addiction treatment for clients with FASD could reduce the overall costs to society.

Knowledge gaps

There are no available economic evaluation studies for FASD in the Netherlands. Recently, the RIVM report, 'Maatschappelijke kosten-batenanalyse van beleidsmaatregelen om alcoholgebruik te verminderen' (Social cost-benefit analysis of regulatory policies to reduce alcohol use in the Netherlands) was published [264]. It is not easy to express all of the costs and benefits of alcohol use in monetary terms, and this is definitely the case for any FASD costs-benefit analyses. Lastly, it is worth noting that these considerations not only influence national government policies, but also policies at a European level.

Recommendations

Based on the limited available evidence, we can surmise that FASD is a serious health problem with high inter-sectoral costs. Interventions focusing on prevention, parent-child assistance programs, and specialized addiction treatment appear to be cost-effective ways of reducing this burden.

3.7. Interventions to Promote Early Detection and to Optimize Management and Care

Current knowledge

Accurate diagnosis of FASD provides the basis for future research aiming to identify developmental trajectories and refine intervention strategies. Until now, too many children in the Netherlands affected by prenatal alcohol exposure are not accurately identified. Examples of how diagnostic processes and associated interventions should be implemented can be found in relation to other diseases in pediatrics such as diabetes type I, obesity, and in relation to many well organized rare disease clinics [265,266].

As elaborated upon in paragraph 2.13, planned health promotion interventions designed to change behavior need to address three issues: correct identification of the desired behaviors and their determinants, the selection and correct application of behavior change methods in an intervention, and adequate implementation of that intervention.

Early Detection. Child and Youth Health Care professionals should consider FASD when evaluating children with developmental problems, behavioral concerns, or school failure. These diagnoses should particularly be considered for children in foster care, especially if drug or alcohol use by a parent contributed to the child being placed in care.

Like other children with complex medical or behavioral disabilities, children with FASD need special attention in terms of the provision and coordination of care, and to ensure that the necessary medical, behavioral, social, and educational services are provided. Early diagnosis of FASD has a protective effect; children who are not diagnosed experience higher rates of secondary problems, including disrupted education, delinquency, institutional confinement, inappropriate sexual behaviors, and alcohol/drug problems [230]. Finally, certain sociodemographic factors should trigger an assessment for an FASD, such as foster care, international adoption, or belonging to known risk groups [236].

Who are the actors for early detection? First, the mother or caretaker. Many children with FASD remain undiagnosed because there is a lack of accurate, routine screening in preventive child and youth health care. As mentioned earlier, early and timely identification of FASD should occur during well-child visits to child health centers. Greater awareness and consistent screening are needed to be effective in identifying and diagnosing FASD [235]. As FASD is not easy to diagnose, and has a wide range of differential diagnoses, it is important to pay continuous attention to the possibility of FASD and especially a good knowledge of the diagnostic criteria. Reasons to miss the diagnosis are insufficient knowledge, time constraints but also fear of stigmatization. More attention needs to be given to the topic of FASD, along with a better education for all caregivers in child health. This needs to start in basic professional and should continue during further specialized training (e.g., for pediatrician, geneticist, child neurologist) and in post-graduate training courses. The translation of existing guidelines into national and local protocols is also necessary (in hospitals but also in the public health field).

What is the evidence for the effectiveness of interventions designed to promote early diagnoses? As far as we know, there is no systematic evidence available to answer this question. The case study from Sweden outlined in the WHO report (2016) [43] suggests the need for the development of materials to both support and train teachers and child health care workers, but the report does not provide information on specific behaviors and determinants. As a consequence, there are no systematic descriptions or evaluations of interventions designed to promote early diagnosis for FASD.

Management and Care. Actors for management and care include parents or other caretakers, teachers, pediatricians and pediatric health care workers, neuropsychologists, psychiatrists, and other child and youth health care professionals involved in the care of an individual with FASD.

What is the evidence for the effectiveness of interventions designed to promote early detection and to optimize management and care? Again, as far as we know, there is no systematic evidence available to answer this question. Studies evaluating the effects of neuropsychological interventions are still limited, and only a very few studies have

investigated their effectiveness and efficacy in individuals prenatally exposed to alcohol [e.g. ,267,268].

In the Netherlands, there are currently no guidelines for the use of interventions once the diagnosis of FASD has been established. Clearly, the Netherlands has good support systems in place for social, psychological, medical and learning disorders but there is no coordination in terms of the management and care of FASD. More research is needed on how to coordinate these efforts in a multidisciplinary fashion.

Lack of knowledge and recommendations

It is obvious that evidence-based knowledge about the early diagnoses of FASD - and in particular the management of and care provided for children with FASD and their caretakers - is insufficient, also in the Netherlands.

Given the complex nature of FASD, it is not only the health system that should be involved, but also other systems such as educational, social, vocational, and justice systems. The need for intervention from infancy onward, and the importance of recognizing and addressing comorbidities, is warranted. Environment modification in order to assist the individual diagnosed within the spectrum of FASD is of utmost importance.

As mentioned earlier, inspiration for establishing good clinical practices - for all professional groups that are involved with prevention and/or management of children and adults with FASD - can be gleaned from looking at recent developments in the Netherlands and in Europe regarding specialized rare disease clinics [265,266]. For infants, children, and adolescents, it is the responsibility of child and youth health care systems (disciplines participating in a multidisciplinary team for the diagnosis of FASD, see paragraph 3.2), not only to provide timely diagnoses and optimal care but also to take the lead when it comes to implementing best practices.

Chapter 4
State of the Art

4. STATE OF THE ART

"Only if you understand the core of FASD problems can you think about solutions"

This chapter summarizes state of the art of FASD challenges as discussed in Chapters 2 and 3. The following topics will be addressed: alcohol consumption, etiology and pathogenesis, biomarkers for alcohol use, genetic factors and alcohol consumption, maternity care, prevalence of FASD, risk behaviors, psychosocial determinants of maternal drinking behavior, environmental conditions, stigma, legal and ethical issues, interventions designed to prevent harm caused by alcohol exposure in pregnancy, FASD diagnosis, neuropsychological testing, neuroimaging, child and youth health care, socioeconomic costs, and interventions designed to promote early detection and to optimize management and care.

Alcohol consumption (paragraph 2.2)

The percentage of women who drink alcohol has increased over time; in the Netherlands, 81.9% of all women drink alcohol [39]. Concern about alcohol use in pregnancy has also increased, but more slowly and much later. The latest data indicate that, in the Netherlands, 8.9% of pregnant women drink alcohol, 6.9% in the first three months of pregnancy and 3.2% after three months [39]. The current health promoting message in most countries recommends abstinence during pregnancy. Binge drinking is especially risky; in the Netherlands, 80.5% of all pregnant women drinking alcohol consumed 1-3 glasses per occasion and 0.8% drank 4 or more glasses per occasion [39,40].

Etiology and pathogenesis (paragraph 2.3)

Ethanol intake of the mother damages the fetus in multiple ways. Beside ethanol and acetaldehyde toxicity, the main effect is increased oxidative stress which triggers several downstream pathways including changes in epigenetic imprinting, gene expression, and metabolite levels. Clinical studies on low to moderate levels of alcohol exposure yield conflicting results, while animal studies with controlled levels of exposure may yield results that are not directly transferable to humans. The main gaps in our knowledge about FASD are a lack of pathophysiological understanding, a lack of agreement on whether there is a safe dose for EtOH intake during pregnancy, and the fact that there are no reliable biomarkers for either FASD detection or estimation of susceptibility, and no cure.

Biomarkers for alcohol use (paragraph 2.4)

Several groups of biomarkers have been discovered in relation to FASD: (1) clinical; (2) molecular; (3) omic; (4) imaging; (5) meconium; (6) cord blood; (7) anatomical; and (8) neurobehavioral biomarkers. Heavy drinkers can be identified using biomarkers of alcohol metabolism or alcohol induced pathophysiology (e.g. EtG, FAEE, PEth) but in the range of low and middle (as well as irregular) consumption, none of the markers

are currently sensitive enough. When it comes to assessment of alcohol abstinence or alcohol consumption in pregnant women, none of the biomarkers is yet reliable enough to estimate the risk of FASD or make a diagnosis of FASD.

Genetic factors and alcohol consumption (paragraph 2.5)

Genetic research contributes to a better understanding of the pathogenesis of FASD. Identifying genetic determinants of drinking patterns may be useful when it comes to identifying biological mechanisms that contribute to specific drinking patterns and to identifying women at risk of alcohol consumption, especially at high levels. Thus, it is important to investigate the role of genomic variation in FASD as related to different levels of alcohol intake. The application of new genetic technologies offers opportunities for using this information in clinical diagnosis and management. In addition, this knowledge is important for prevention. Prevention strategies for moderating and stopping alcohol consumption in women before and during pregnancy may target these pathogenetic mechanisms and may be directed towards individuals at high risk of alcohol consumption due to genetic predisposition. The recommendation for researchers is to focus upon the translation of basic genetic research into clinical practice and to unravel the complex interactions between genes, brain and behavior.

Maternity care (paragraph 2.6)

Maternity care is well organized in the Netherlands. What is remarkable is the neglect of issues concerning FASD prevention, diagnosis and treatment within the knowledge system of maternity care. Maternity care workers - stakeholders - should actively address the topic of alcohol exposure before, during, and after pregnancy, and feel responsible for collecting reliable data about alcohol consumption during pregnancy. It would make sense to use the existing maternity care knowledge infrastructure and for stakeholders to join forces to develop screening and (brief) evidence-based intervention programs.

Prevalence of FASD (paragraph 2.7)

The first publications on the harmful effects of prenatal alcohol exposure date from 1968 and 1973. Because FASD is a birth defect, we use the term prevalence instead of incidence. Prevalence rates of FASD within the general population, as reported in a recently conducted systematic meta-analysis (Roozen et al. 2016) were only available for 10 countries (data were not available for the Netherlands); prevalence estimates varied from 0 to 176.77 per 1,000 livebirths worldwide. For FAS, the global prevalence rate was estimated to be 2.89 per 1,000 livebirths [85]. Popova and colleagues [42] estimated a global FAS prevalence rate of 14.6 per 10,000 livebirths and FAS prevalence rates in Europe of 37.4 per 10,000 livebirths. The figures of these recent studies should, however, be interpreted with caution, given the limitations of the available data.

In the Netherlands, there is no structured surveillance system that monitors FASD, and therefore no reliable data are available. The recommendation is to follow the BMA (2016) guidelines [15] to determine populations at risk, and to implement uniform diagnostic criteria for FASD using the recently updated clinical guidelines proposed by Hoyme and colleagues (2016) [14].

Risk Behaviors (paragraph 2.8)

Health promotion messages designed to prevent prenatal alcohol exposure should be based on epidemiological data identifying which specific prenatal alcohol drinking behaviors lead to risk. That knowledge is currently limited. The main reason for this is that studies use various techniques and implement them in different ways, so that comparisons across studies are difficult and drawing general conclusions is not justified. Moreover, meta-analyses are impossible. This is also why all the current guidelines (e.g., WHO, BMA, Dutch Health Council) suggest abstinence during pregnancy as the only safe advice. However, more attention needs to be given to women who drink alcohol during pregnancy, with special attention for specific risk groups such as pregnant women who drink heavily. One recommendation is for researchers to make sure that their measures of alcohol use are comparable to measures in other studies. Moreover, to date, the designs of almost all of these studies have been retrospective, and there is a need for more prospective studies.

Psychosocial determinants of maternal drinking behavior (paragraph 2.9)

In terms of behavioral change, it is necessary to understand the determinants of the behavior and their underlying beliefs. In summary, research on determinants of maternal drinking shows that there are negative associations between maternal drinking and risk perception beliefs about harm to the unborn baby, attitudinal beliefs about advantages of not-drinking for the baby, normative beliefs of the partner and of midwives, and self-efficacy beliefs regarding abstaining. There are positive relationships between maternal drinking and the risk perception belief that only larger amounts of alcohol will hurt the baby, the attitudinal belief that not-drinking has disadvantages (e.g. stress), the alcohol intake of the partner, self-efficacy beliefs related to negative emotions, higher habitual alcohol intake before pregnancy, and cue-reactivity related to alcohol. On the whole, the literature on determinants is limited. The research methods utilized are too simple and many potentially relevant determinants are not investigated. Most studies focus on pregnant women and ignore women who might be pregnant as well as unplanned pregnancies. The only Dutch study of high quality and showing a comparable pattern of results is listed above [118].

Environmental conditions (paragraph 2.10)

Women who are - or may be - pregnant, the child with FASD, caretakers, and child and youth health professionals are all embedded in a social and physical environment that

influences their behaviors and the determinants of those behaviors. Environmental conditions are controlled by decision-makers at the interpersonal (e.g. partner), organizational (e.g. YHC), community (e.g. school) and policy (e.g. alcohol marketing) levels. There has been almost no systematic research on these agents, their behavior, or the determinants of their behavior. One Dutch study showed that pregnant women received the abstinence message from their midwife but only reactively, while alcohol use was not systematically screened. Pregnant women who drink receive conflicting advice about alcohol from midwives and general practitioners [137]. The recommendation is to identify environmental conditions related to maternal drinking, and identify who the relevant decision-makers are, following a theory- and evidence-based procedure.

Stigma (paragraph 2.11)

Stigmatization is a process by which a person is identified as different and then devaluated. Public stigma of women who use (or have used) alcohol during pregnancy results in blaming and shaming. Well-intended information about the biological explanations for alcohol dependence may in fact contribute to public stigma. Children and youth with FASD can be misunderstood, disrespected and blamed, as they are often held responsible for their inability to offset the negative impact of FASD by, for example, controlling their behaviors or 'acting their age'. Mothers of children with FASD may hold themselves accountable, leading to self-stigma, and these women may not acknowledge the relevant social and cultural influences contributing to their alcohol use. Associates of children and youth with FASD and their mothers are also subjected to stigmatization. Non-biological parents may feel compelled to disclose that their child was adopted. Structural stigma is reflected in the criminalization of women who drink alcohol during pregnancy. Even well-intended health promotion messages may contribute to structural stigmatization. Fear of stigmatization is therefore an impediment to the prevention of prenatal exposure to alcohol. The recommendation is to systematically investigate the beliefs underlying stigmatization - as well as the structures that contribute to stigmatization - in order to develop interventions aimed at decreasing the amount of stigmatization.

Legal and ethical issues (paragraph 2.12)

It is clear that alcohol problems should be investigated within a broader context of lifestyle and environmental conditions. There is a need for a more appropriate understanding of the complexity of the topic and the dynamics of policy discussions within society. Simply blaming the mother and (unborn) child is a pitfall that we shouldn't fall into. Legal and ethical considerations can contribute to our understanding and should be used as tools for influencing policy discussions.

Interventions designed to prevent harm caused by alcohol exposure in pregnancy (paragraph 2.13) should be further developed.

In order to develop effective interventions, we need to (1) identify the relevant target behaviors and their determinants, (2) apply appropriate behavior change methodologies, and (3) adequately implement the intervention. The range of interventions currently available is poor, due to the low quality of intervention studies. A 2016 WHO report [43] documents case studies from the Member States. The report mentions that half of the pregnancies in Europe are unplanned and that our knowledge on determinants is limited. The growing influence of alcohol marketing targeting women is recognized, and the WHO recommends the routine collection of FASD data in all Member States. Public health promotion interventions targeting alcohol consumption will also impact prenatal alcohol exposure. Effectively using contraception can also prevent prenatal alcohol exposure. The evidence for the effects of interventions targeting pregnant women is limited, although suggests a potentially positive effect of simply assessing alcohol intake. A Dutch study on training midwives suggests that a counselling intervention as well as an eHealth intervention may contribute to reduced drinking in pregnant women, and that the eHealth intervention may be more cost-effective [179,180]. There is a lack of interventions based in theory and evidence, despite research showing that promoting risk awareness should always be combined with increasing self-efficacy in order to have the desired effect. The Intervention Mapping protocol provides the means for planning theory- and evidence-based health promotion interventions.

FASD Diagnosis (paragraph 3.2)

When it comes to FASD diagnosis, the search continues for appropriate methodology that can be used to measure key features of FAS (e.g., structural abnormalities, neurodevelopmental deficits). There are several different guidelines available for making a diagnosis in the FASD spectrum. However, there is no agreement on a universal diagnostic system for FASD. Diagnosis of FASD requires a multidisciplinary approach, and guidelines should be developed by the professional associations involved. Multidisciplinary evidence-based guidelines can be developed within the existing tradition of guideline development used in the Dutch health care system. The recommendation is to develop these guidelines and implement them in clinical practice.

Neuropsychological testing (paragraph 3.3)

Neuropsychological testing is important for the diagnosis and treatment of individuals prenatally exposed to alcohol. Research should use tests measuring cognition, motivation, and/or temporal processing. Moreover, research should focus on the validity of these tests (in relation to FASD) in a developmental context, and norm data should be collected for representative standardization samples.

Neuroimaging (paragraph 3.4)

Many technological advances have been made over the last decades in terms of ways in which to examine the structure and function of the brain. Several different neuroimaging techniques have been applied to study individuals prenatally exposed to alcohol, particularly MEG, PET, SPECT, and MRI, each with their own benefits and restrictions. These techniques are of great potential value, both in terms of understanding the cognitive deficits exhibited in individuals affected by FASD, as well as in relation to future treatments for individuals prenatally exposed to alcohol. The knowledge that different cognitive strategies may be utilized by individuals with FASD may suggest the need for different treatment approaches to build on the cognitive strategies that individuals with FASD are already using.

Child and youth health care (paragraph 3.5)

Pediatrics. Registration of FASD in the Netherlands is almost non-existent and should be improved. Pediatricians may miss the FASD diagnosis because of insufficient knowledge or time constraints but also due to fear of stigmatization. It is highly recommended that pediatricians and their professional associations take an active role in the diagnosis of FASD.

Child and youth health care (CYHC). The report by the Dutch Health Council (2005) mentioned the negative effects of prenatal alcohol exposure and FAS [38]. The report did not address the role of child and youth health care in reducing morbidity related to FASD. The CYHC centers have a high coverage and see almost all children repeatedly over their lifespan. Currently, child and youth health care contributes to primary prevention by increasing awareness through school programs, helping adolescents to develop the skills to make responsible choices (thereby also preventing unintended pregnancies), and focusing on non-pregnant women at risk (e.g. women who have already had a child with FASD). Early diagnosis of FASD has a protective effect. The recommendation is to promote health professionals' awareness of considering FASD when evaluating children with problem behaviors.

Socio-economic costs (paragraph 3.6)

The high prevalence of FASD places an immense financial burden on society in terms of unrealized productivity and human suffering. There are three economic evaluation studies [261–263] which have explored the cost-effectiveness of interventions for FASD. These studies concluded that these interventions were cost-effective. There are no available economic evaluation studies for FASD in the Netherlands. We recommend that the financial burden FASD places on society is systematically investigated. In addition, it is recommended that the inter-sectoral costs and benefits of FASD prevention are investigated.

Interventions to promote early detection and to optimize management and care (paragraph 3.7)

Globally, and in the Netherlands, evidence-based knowledge about early diagnosis of FASD and the management and care of children with FASD is insufficient. It is important to identify the relevant decision-makers or stakeholders responsible for early diagnosis and optimal management and care. There has been insufficient research carried out on interventions to promote early detection and optimize management and care. Cross-sectoral cooperation between different systems (e.g., educational and justice systems) is essential for the development of good clinical practice. This should be for the aim of all professional groups that are involved with prevention and management of children and adults with FASD.

Chapter 5
Setting Priorities & Conclusion

5. SETTING PRIORITIES & CONCLUSION

Based on the current state of the art, what are the priorities for FASD prevention and care in the Netherlands? A *dual-track policy* would appear to be the best approach, consisting of: 1. short-term consensus and action directed at prevention, early detection and care, combined with 2. a longer-term research and reflection program. At least four groups of actors and actions are involved in these priorities:

(a) Women/mothers/caretakers/foster parents,

(b) Child and youth healthcare workers,

(c) Government

(d) Researchers.

The short-term action, priority 1, focuses on translating current knowledge into current practice; our knowledge is indeed limited, but at the same time, we know much more than what is currently applied in practice. The various professionals involved, and their organizations, should develop guidelines for best practice in terms of prevention, early diagnosis, management and care. Other areas of research can provide good examples of how to build consensus within a group of professionals, and reach agreement on best practices. The government should systematically stimulate and support these processes within the relevant professional organizations.

The longer-term research and development activities, priority 2, should focus on the specific Dutch setting - the norms and characteristics of our health care system. There is a need for theory- and evidence-based development of (a) more effective prevention messages, as well as (b) training programs for all professionals involved in communication with women, mothers, caretakers and foster parents. The issue of stigma reduction is particularly relevant in both proposed research programs, taking into account the first recommendation from an ethical perspective: promoting the welfare of children with FASD.

Table 5 provides an overview of current priority questions. The priority scores indicate support for the proposed dual-track policy: short-term consensus on action and longer-term research for improvement of prevention as well as early diagnosis and provision of care.

Conclusion

Priority 1: Short-term consensus and action directed at prevention, early detection and care

1.1 The short-term consensus should first focus on the healthcare workers involved in prevention, early detection, management and care, urging them to decide on best practice and optimal task division, while dealing effectively with stigma and ethical challenges.

1.2 Secondly, focus should turn to what we know about etiology, prevalence and effective interventions to prevent FASD, especially in high-risk groups.

1.3 The Government should actively promote and support these activities.

Priority 2: Longer-term research and reflection program.

2.1 In the longer-term, a theory- and evidence-based research program should contribute to the systematic development of health promotion interventions directed at women before they get pregnant, those planning to get pregnant and pregnant women, as well as high-risk groups (e.g., binge drinking women), in order to optimize the message of not drinking.

2.2 A second research priority should focus on the optimal implementation of best practices in the prevention, early diagnosis, management and care of FAS. Here, again, the outcomes depend upon effectively dealing with stigma and ethical challenges, and empowering women, mothers and caretakers to cope with a difficult behavior change.

Table 5 Overview of Priority Questions

Rank order	10: very high, 1: very low	Importance	Changeability
	Women/mothers/caretakers/foster parents:		
11	Risk groups for prevention: Unplanned, planning, pregnant; binge drinking, low SES, child with FASD	7.6	6.4
10	Complex abstinence message: Stress/scared, evidence, binge drinking double message for CYHC; dealing with stigma – supported by communication experts	7.5	6.5
5	Theory & evidence: Limited in terms of etiology, prevalence, and effective interventions to prevent FASD; especially about risk groups	8.2	6.6
3	Dual-track policy: Consensus on action & research for improvement	8.1	7.2
	Child and youth health care:		
2	CYHC: Decide via consensus on best practice, including who is responsible, dealing with stigma, and ethical issues – supported by implementation experts	8.5	7.2
	Government:		
9	Decide who is responsible for which activity around FASD: Registration, prevention, early diagnosis and optimal treatment	7.3	6.8
8	Public education for prevention: Double message; preventing stigma and stress	7.9	6.7
12	Policies for reducing alcohol use in the general population, especially binge drinking	8.0	5.7
4	Urging decision making in CYHC on best practices in terms of FASD	7.8	7.1
7	Dual-track policy: Short-term action & longer-term improvement, based on theory and evidence - biomedical & behavioral science research	8.0	6.7
	Research:		
1	Public education prevention message: pre-pregnancy, risk groups, double message, stigma	8.4	7.4
6	Child and youth health care setting: optimal health promotion interaction for early diagnosis and treatment	7.9	6.8

Note The scores reflect the average scores from *n* = 35 experts who were present during a national stakeholder meeting. Scores were provided for the importance and changeability of each of the prioritized knowledge question areas.

Samenvatting

Deze kennissynthese heeft als onderwerp Foetal Alcohol Spectrum Stoornis (FASD). De ontwikkeling van het ongeboren kind komt in gevaar door consumptie van alcohol door de moeder tijdens de zwangerschap. FASD is de overkoepelende term voor geboorteafwijkingen ten gevolge van prenatale blootstelling aan de stof ethanol. Het handelt hier om een belangrijk en schrijnend probleem, des te meer daar de gezondheidsproblemen van het (on)geboren kind te voorkomen zijn.

Over de omvang en ernst van het probleem weten wij nog te weinig. Ook schiet onze kennis over diagnostiek, behandeling en begeleiding tekort. FASD is één van de belangrijkste te voorkomen oorzaken van een verstandelijke handicap. De Nederlandse Gezondheidsraad concludeerde al in 2005 dat wij nog te weinig weten over welk drinkgedrag nu schadelijk is voor het ongeboren kind.

Het opstellen van een kennissynthese over Foetaal Alcohol Syndroom (FASD) is noodzakelijk voor interventieprogramma's, vervolgonderzoek en beleid.

FASD is een te voorkomen aandoening. Maar om uiteindelijk effectieve interventies te ontwikkelen is een zorgvuldig planningsproces noodzakelijk. Intervention Mapping (IM) is zo'n planningsproces. In de kennissynthese wordt aan de hand van het IM protocol over door ZonMw geformuleerde FASD kennisvragen met betrekking tot de omvang van het probleem (prevalentie/incidentie), het vermijden van het probleem (preventie) en het inventariseren van bestaande knelpunten rond diagnostiek, begeleiding en behandeling, nader gerapporteerd.

De Kennissynthese omvat 5 hoofdstukken. Na een korte uitleg over IM en het noemen van de door ZonMw geformuleerde vragen over FASD (hoofdstuk 1) gaat de aandacht in hoofdstuk 2 uit naar primaire preventie en in hoofdstuk 3 naar secondaire en tertiaire preventie. Hoofdstuk 4 'State of the Art' betreft een samenvatting van de huidige stand van zaken rond de in hoofdstuk 2 en 3 besproken thema's. Aan de orde komen: alcohol consumptie, etiologie en pathogenese, biomarkers voor alcohol gebruik, genetische factoren, preconceptiezorg, prevalentie, risicogedrag, psycho-sociale determinanten van drinkgedrag, omgeving condities, stigma, juridische en ethische aspecten

en interventies om schade veroorzaakt door blootstelling aan alcohol in zwangerschap te voorkomen.

Op basis van huidige kennis en gesignaleerde tekortkomingen zoals besproken in hoofdstuk 2, 3 en 4 wordt in hoofdstuk 5 aandacht besteed aan de prioritering van FASD gerelateerde onderzoeksvragen. Naast relevantie wordt tevens haalbaarheid voor verandering in ogenschouw genomen. Geconcludeerd wordt dat FASD preventie en zorg in Nederland gebaat is met een tweesporenbeleid: voor de korte termijn het ondernemen van acties gericht op preventie, vroege detectie en zorg gecombineerd met op de lange termijn de nodige aandacht voor verder onderzoek en reflectie op deze complexe problematiek. Acties op korte termijn dienen gericht te zijn op het vertalen van reeds aanwezige kennis en inzichten naar de huidige zorgpraktijk. Er is immers kennis voor handen waar de zorgpraktijk direct bij gebaat is. Een langere termijn onderzoeksprogramma kan de zorgpraktijk verbeteren door planmatige toepassing van theorie en evidentie bij zowel preventie als diagnostiek, begeleiding en behandeling.

References

1. O'Leary CM, Nassar N, Kurinczuk JJ, de Klerk N, Geelhoed E, Elliott EJ, et al. Prenatal alcohol exposure and risk of birth defects. Pediatrics. 2010;126:e843-50.
2. May PA, Gossage JP, White-Country M, Goodhart K, Decoteau S, Trujillo PM, et al. Alcohol consumption and other maternal risk factors for fetal alcohol syndrome among three distinct samples of women before, during, and after pregnancy: the risk is relative. Am. J. Med. Genet. C. Semin. Med. Genet. 2004;127C:10–20.
3. Morleo M, Woolfall K, Dedman D, Mukherjee R, Bellis MA, Cook PA. Under-reporting of foetal alcohol spectrum disorders: an analysis of hospital episode statistics. BMC Pediatr. BioMed Central Ltd; 2011;11:14.
4. World Health Organization. European action plan to reduce the harmful use of alcohol 2012–2020. Copenhagen; 2012.
5. World Health Organization. Global status report on alcohol and health-2014. Copenhagen; 2014.
6. World Health Organization. Alcohol in the European Union. Consumption, harm and policy approaches. Copenhagen; 2012.
7. May PA, Blankenship J, Marais AS, Gossage JP, Kalberg WO, Barnard R, et al. Approaching the Prevalence of the Full Spectrum of Fetal Alcohol Spectrum Disorders in a South African Population-Based Study. Alcohol. Clin. Exp. Res. 2013;37:818–30.
8. Landgren M, Svensson L, Strömland K, Andersson Grönlund M. Prenatal alcohol exposure and neurodevelopmental disorders in children adopted from eastern Europe. Pediatrics. 2010;125:e1178-85.
9. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5). Washington DC; 2013.
10. Harris JC. New classification for neurodevelopmental disorders in DSM-5. Curr. Opin. Psychiatry. 2014;27:95–7.
11. Hagan JF, Balachova T, Bertrand J, Chasnoff I, Dang E, Fernandez-Baca D, et al. Neurobehavioral Disorder Associated With Prenatal Alcohol Exposure. Pediatrics. 2016;138.
12. Abel EL, Sokol RJ. Incidence of fetal alcohol syndrome and economic impact of FAS-related anomalies. Drug Alcohol Depend. 1987;19:51–70.
13. Abel EL, Sokol RJ. Fetal alcohol syndrome is now leading cause of mental retardation. Lancet. 1986;328:1222.
14. Hoyme, H.E., Kalberg, W.O., Elliott, A.J., Blankenship, J., Buckley, D., Marais, A.S., Manning, M.A., Robinson, L.K., Adam, M.P., Abdul-Rahman, O. and Jewett T. Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. Pediatrics. 2016;138.
15. British Medical Association. Alcohol and pregnancy Preventing and managing fetal alcohol spectrum disorders, june 2007, updated february 2016. 2016.
16. Bartholomew Eldredge LK, Markham C, Ruiter RAC, Fernandez M, Kok G. Planning health promotion programs: an Intervention Mapping approach. John Wiley & Sons; 2016.

17. Kok G, Gottlieb NH, Peters G-JY, Mullen PD, Parcel GS, Ruiter RAC, et al. A Taxonomy of Behavior Change Methods; an Intervention Mapping Approach. Health Psychol. Rev. Taylor & Francis; 2015;31:1–32.
18. Roozen S, Black D, Peters G-JY, Kok G, Townend D, Nijhuis JG, et al. Fetal Alcohol Spectrum Disorders (FASD): an Approach to Effective Prevention. Curr. Dev. Disord. Reports. Current Developmental Disorders Reports; 2016;3:229–34.
19. Carpenter B, Blackburn C, Egerton J. A brief introduction to fetal alcohol spectrum disorders. In: Carpenter B, Blackburn C, Egerton J, editors. Fetal alcohol Spectr. Disord. Interdiscip. Perspect. New York: Routledge; 2013. p. 3.
20. Abel EL, Sokol RJ. A revised conservative estimate of the incidence of FAS and its economic impact. Alcohol. Clin. Exp. Res. 1991;15:514–24.
21. Popova S, Stade B, Bekmuradov D, Lange S, Rehm J. What do we know about the economic impact of fetal alcohol spectrum disorder? A systematic literature review. Alcohol Alcohol. 2011;46:490–7.
22. Thanh NX, Jonsson E. Costs of fetal alcohol spectrum disorder in Alberta, Canada. Can. J. Clin. Pharmacol. 2009;16:e80–90.
23. Koren G, Nulman I, Chudley AE, Loocke C. Fetal alcohol spectrum disorder. CMAJ. 2003;169:1181–5.
24. Health Council of the Netherlands. Preconception care: for a good beginning. The Hague; 2007.
25. BBC series. Inspector_Lynley_Mysteries. A Cry for Justice. 2004.
26. Golden J. Message in a bottle. The making of fetal alcohol syndrome. Cambridge: Harvard University Press; 2005.
27. Van Laar MW, Van Ooyen-Houben MMJ. Nationale drug monitor jaarbericht 2015. Trimbos-instituut. 2015.
28. Lemmens P. Relationship of alcohol consumption and alcohol problems at the population level. In: Heather N, Peters TJ, Stockwell T, editors. Int. Handb. alcohol Depend. Probl. Chichester: Wiley; 2001.
29. Lemoine P, Harousseau H, Borteyru JP, Menuet JC. Les enfants des parents alcoholiques: anomolies observees a propos de 127 cas. Ouest méd. 1968;21:476–82.
30. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. Lancet. 1973;302:999–1001.
31. Armstrong EM, Abel EL. Fetal alcohol syndrome: the origins of a moral panic. Alcohol Alcohol. 2000;35:276–82.
32. Drabble LA, Poole N, Magri R, Tumwesiguy NM, Qing. L, Plant M. Conceiving risk, divergent Responses: Perspectives on the evolution of the construction of FASD in six countries. Subst. Use Misuse. 2011;46:943–58.
33. ICAP. International Guidelines on Drinking and Pregnancy. 2009.
34. Raad voor Strafrechtstoepassing en Jeugdbescherming. Advies Prenatale kinderbescherming en de rol van de overheid. Den Haag; 2015.
35. De Wert G, Berghmans R. Neem zwangere verslaafde vroeger op. Schade door alcohol of drugs bij het kind is er al voor de 24ste week. NRC-Handelsblad. 2009 Jan 9;9.
36. Hondius AJK, Stikker TE, Wennink JMB, Honig A. Wet BOPZ toegepast bij vroege zwangerschap van verslaafde. Ned. Tijdschr. Geneeskd. 2011;155.
37. Tholen J, Siero S. Alcoholgebruik tijdens de zwangerschap. Tijdschr. voor Soc. gezondheidszorg. 1989;67:149.
38. Health Council of the Netherlands. Risks of alcohol consumption related to conception, pregnancy and breastfeeding. The Hague; 2005.
39. Lanting CI, van Wouwe JP, Van Dommelen P, De Josselin de Jong S, Kleinjan M, Van Laar M. Factsheet “Alcoholgebruik tijdens zwangerschap en borstvoeding.” TNO en Trimbos Instituut; 2015.
40. Lanting CI, van Dommelen P, van der Pal-de Bruin KM, Bennebroek Gravenhorst J, van Wouwe JP. Prevalence and pattern of alcohol consumption during pregnancy in the Netherlands. BMC Public Health. 2015;15.
41. ZonMw. Zwangerschap en geboorte Een impressie van het kennisnetwerk geboortezorg en onderzoeksprojecten [Internet]. 2014. Available from: www.zonmw.nl/zwangerschapengeboorte

42. Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. Lancet Glob. Heal. 2017;1–10.
43. Schölin L. Prevention of harm caused by alcohol exposure in pregnancy. Copenhagen; 2016.
44. Koop DR. Alcohol metabolism's damaging effects on the cell. Alcohol Res Heal. 2006;29:274–80.
45. Gupta KK, Gupta VK, Shirasaka T. An Update on Fetal Alcohol Syndrome - Pathogenesis, Risks, and Treatment. Alcohol. Clin. Exp. Res. 2016;40:1594–602.
46. Sarkar DK. Male germline transmits fetal alcohol epigenetic marks for multiple generations: A review. Addict. Biol. 2016;21:23–34.
47. Porter NA. Chemistry of lipid peroxidation. Methods Enzymol. 1984;105:273–82.
48. Eijkelenboom A, Burgering BMT. FOXOs: signalling integrators for homeostasis maintenance. Nat. Rev. Mol. Cell Biol. Nature Publishing Group; 2013;14:83–97.
49. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Database Syst. Rev. 2008;
50. Mathew MC, Ervin A-M, Tao J, Davis RM. Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract. Cochrane database Syst. Rev. 2012;6:CD004567.
51. Bjelakovic G, Ll G, Nikolova D, Bjelakovic M, Nagorni A, Gluud C, et al. Antioxidant supplements for liver diseases. Cochrane Database Syst Rev. 2011;16:3–5.
52. Eberhart JK, Parnell SE. The Genetics of Fetal Alcohol Spectrum Disorders. Alcohol. Clin. Exp. Res. 2016;40:1154–65.
53. Chokroborty-Hoque A, Alberry B, Singh SM. Exploring the complexity of intellectual disability in fetal alcohol spectrum disorders. Front. Pediatr. 2014;2:90.
54. Wu D, Cederbaum AI. Alcohol, oxidative stress, and free radical damage. Alcohol Res. Heal. 2003;27:277–84.
55. Wilkinson MD, Dumontier M, Aalbersberg IjJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci. Data. 2016;3:160018.
56. Lapatas V, Stefanidakis M, Jimenez RC, Via A, Schneider MV. Data integration in biological research: an overview. J. Biol. Res. (Thessalonikē, Greece). Journal of Biological Research-Thessaloniki; 2015;22:9.
57. Bearer CF, Stoler JM, Cook JD, Carpenter SJ. Biomarkers of alcohol use in pregnancy. Alcohol Res. Heal. 2004;28:38–43.
58. Chabenne A, Moon C, Ojo C, Khogali A, Nepal B, Sharma S. Biomarkers in fetal alcohol syndrome. Biomarkers Genomic Med. Elsevier Taiwan LLC and the; 2014;6:12–22.
59. Wassenaar S, Sibbles BJ, Schneider AJT, Aaldriks AA. Testen op alcoholgebruik in de zwangerschap. Welke biomarkers zijn geschikt? Ned. Tijdschr. Geneeskd. 2016;160:1–5.
60. Bakhireva LN, Savage DD. Focus on: biomarkers of fetal alcohol exposure and fetal alcohol effects. Alcohol Res. Heal. 2011;34:56.
61. Balaraman S, Schafer JJ, Tseng AM, Wertelecki W, Yevtushok L, Zymak-Zakutnya, N., Chambers CD, et al. Plasma miRNA Profiles in Pregnant Women Predict Infant Outcomes following Prenatal Alcohol Exposure. PLoS One. 2016;11.
62. Montag AC, Hull AD, Yevtushok L, Zymak-Zakutnya N, Sosyniuk Z, Dolhov V, et al. Second-Trimester Ultrasound as a Tool for Early Detection of Fetal Alcohol Spectrum Disorders. Alcohol. Clin. Exp. Res. 2016;40:2418–25.
63. Mesa DA, Kable JA, Coles CD, Jones KL, Yevtushok L, Kulikovsky Y, et al. The Use of Cardiac Orienting Responses as an Early and Scalable Biomarker of Alcohol-Related Neurodevelopmental Impairment. Alcohol. Clin. Exp. Res. 2017;41:128–38.
64. Tseng PH, Cameron IGM, Pari G, Reynolds JN, Munoz DP, Itti L. High-throughput classification of clinical populations from natural viewing eye movements. J. Neurol. 2013;260:275–84.
65. Mandal C, Kim SH, Chai JC, Oh SM, Lee YS, Jung KH, et al. RNA Sequencing Reveals the Alteration of the Expression of Novel Genes in Ethanol-Treated Embryoid Bodies. PLoS One. 2016;11:e0149976.

66. Kapoor M, Wang JC, Wetherill L, Le N, Bertelsen S, Hinrichs AL, et al. A meta-analysis of two genome-wide association studies to identify novel loci for maximum number of alcoholic drinks. Hum. Genet. 2013;132:1141–51.
67. Kutalik Z, Benyamin B, Bergmann S, Mooser V, Waeber G, Montgomery GW, et al. Genome-wide association study identifies two loci strongly affecting transferrin glycosylation. Hum. Mol. Genet. 2011;20:3710–7.
68. Clark SL, Aberg KA, Nerella S, Kumar G, Mcclay JL, Chen W, et al. Combined Whole Methylome and Genomewide Association Study Implicates CNTN4 in Alcohol Use. Alcohol. Clin. Exp. Res. 2015;39:1396–405.
69. Mimmack ML, Saito H, Evans G, Bresler M, Keverne EB, Emson PC. A novel splice variant of the cell adhesion molecule BIG-2 is expressed in the olfactory and vomeronasal neuroepithelia. Mol. Brain Res. 1997;47:345–50.
70. Feeney E, O'Brien S, Scannell A, Markey A, Gibney ER. Genetic variation in taste perception: does it have a role in healthy eating? Proc Nutr Soc. 2011;70:135–43.
71. Duffy, V.B., Davidson, A.C., Kidd, J.R., Kidd, K.K., Speed, W.C., Pakstis, A.J., Reed, D.R., Snyder, D.J. and Bartoshuk LM. Bitter receptor gene (TAS2R38), 6-n-Propylthiouracil (PROP) Bitterness and Alcohol Intake. Alcohol Clin Exp Res. 2004;28:1629–1637.
72. Hayes JE, Wallace MR, Knopik VS, Herbstman DM, Bartoshuk LM, Duffy VB. Allelic variation in TAS2R bitter receptor genes associates with variation in sensations from and ingestive behaviors toward common bitter beverages in adults. Chem. Senses. 2011;36:311–9.
73. Wang JC, Hinrichs AL, Bertelsen S, Stock H, Budde JP, Dick DM, et al. Functional variants in TAS2R38 and TAS2R16 influence alcohol consumption in high-risk families of African-American origin. Alcohol. Clin. Exp. Res. 2007;31:209–15.
74. Keller M, Liu X, Wohland T, Rohde K, Gast MT, Stumvoll M, et al. TAS2R38 and its influence on smoking behavior and glucose homeostasis in the German sorbs. PLoS One. 2013;8:4–9.
75. Timpson NJ, Christensen M, Lawlor D a, Gaunt TR, Day IN, Ebrahim S, et al. traits , and eating behavior in the British Women ' s Heart and Health. Am. J. Clin. Nutr. 2005;81:1005–11.
76. Carrai M, Steinke V, Vodicka P, Pardini B, Rahner N, Holinski-Feder E, et al. Association between TAS2R38 gene polymorphisms and colorectal cancer risk: A case-control study in two independent populations of caucasian origin. PLoS One. 2011;6.
77. Hurley TD, Edenberg HJ. Genes encoding enzymes involved in ethanol metabolism. Alcohol Res. 2012;34:339–44.
78. Taylor M, Simpkin AJ, Haycock PC, Dudbridge F, Zuccolo L. Exploration of a polygenic risk score for alcohol consumption: A longitudinal analysis from the ALSPAC cohort. PLoS One. 2016;11:1–15.
79. Midwifery in The Netherlands. R. Dutch Organ. midwives. 2014.
80. ZonMw. Zwangerschap en geboorte. Een gezonde start voor moeder en kind. 2016.
81. Werkgroep MDR. Multidisciplinaire Richtlijn Stoornissen in het gebruik van Alcohol. 2009.
82. Noteborn W. Alcohol ? Even niet !? Tijdschr. voor Verlos. 2014;7:54–6.
83. Van der Wulp NY, Hoving C, de Vries H. Dutch midwives' experiences with implementing health counselling to prevent prenatal alcohol use. J. Clin. Nurs. 2014;1–4.
84. Mason CA, Kirby RS, Sever LE, Langlois PH. Prevalence is the preferred measure of frequency of birth defects. Birth Defects Res. Part A - Clin. Mol. Teratol. 2005;73:690–2.
85. Roozen S, Peters G-JY, Kok G, Townend D, Nijhuis J, Curfs L. Worldwide Prevalence of Fetal Alcohol Spectrum Disorders: A Systematic Literature Review Including Meta-Analysis. Alcohol. Clin. Exp. Res. 2016;40:18–32.
86. Popova S, Lange S, Probst C, Parunashvili N, Rehm J. Prevalence of alcohol consumption during pregnancy and Fetal Alcohol Spectrum Disorders among the general and aboriginal populations in Canada and the United States. Eur. J. Med. Genet. Elsevier Ltd; 2016;
87. Pereira, R. R., Rijpstra A, van Putten DM, Projectnaam NSCK. Jaarverslag Nederlands Signalerings-centrum Kindergeneeskunde 2012. 2012.

88. Abdelmalik N, van Haelst M, Mancini G, Schrander-Stumpel C, Marcus-Soekarman D, Hennekam R, et al. Diagnostic outcomes of 27 children referred by pediatricians to a genetics clinic in the Netherlands with suspicion of fetal alcohol spectrum disorders. Am. J. Med. Genet. A. 2013;161A:254–60.
89. Swelheim H, Flapper B, van Balkom I. De diagnostiek van FASD, een multidisciplinaire aanpak. Prakt. Pediatr. 2014;4:248–51.
90. Roozen S, Peters G-JY, Kok G, Townend D, Nijhuis J, Koek G, et al. Which parental alcohol-related behaviors are related to Fetal Alcohol Spectrum Disorders (FASD)? A question that cannot be answered yet. Manuscr. Prep.
91. Jentink J, Zetstra-van der Woude AP, Bos J, de Jong-van den Berg LTW. Evaluation of the representativeness of a Dutch non-malformed control group for the general pregnant population: are these controls useful for EUROCAT? Pharmacoepidemiol. Drug Saf. 2011;20:1217–23.
92. Verkerk PH, Van Noord-Zaanstra BM, Florey CV, De Jonge GA, Verloove-Vanhorick SP. The effect of moderate maternal alcohol consumption on birth weight and gestational age in a low risk population. Early Hum. Dev. 1993;32:121–9.
93. Knottnerus JA, Delgado LR, Knipschild PG, Essed GGM, Smits F. Haematologic parameters and pregnancy outcome. J. clin. epidemiol. 1990;43:461–6.
94. Vonsee HJ, Stobberingh EE, Bouckaert PX, Van den Bogaard AE. Frequency of Chlamydia trachomatis, Mycoplasma hominis and Ureaplasma urealyticum infections in pregnant women. J. Chemother. 1989;1:904–5.
95. Lanting CI, Buitendijk SE, Crone MR, Segaar D, Gravenhorst JB, van Wouwe JP. Clustering of socioeconomic, behavioural, and neonatal risk factors for infant health in pregnant smokers. PLoS One. 2009;4:1–6.
96. Bakker R, Pluimgraaff LE, Steegers EAP, Raat H, Tiemeier H, Hofman A, et al. Associations of light and moderate maternal alcohol consumption with fetal growth characteristics in different periods of pregnancy: the Generation R Study. Int. J. Epidemiol. 2010;39:777–89.
97. Goedhart G, Van Eijsden M, Van Der Wal MF, Bonsel GJ. Ethnic differences in term birthweight: The role of constitutional and environmental factors. Paediatr. Perinat. Epidemiol. 2008;22:360–8.
98. Pfinder M, Kunst AE, Feldmann R, van Eijsden M, Vrijkotte TGM. Preterm birth and small for gestational age in relation to alcohol consumption during pregnancy: stronger associations among vulnerable women? results from two large Western-European studies. BMC Pregnancy Childbirth. 2013;13:49.
99. Mutsaerts MAQ, Groen H, Buiter-Van Der Meer A, Sijtsma A, Sauer PJJ, Land JA, et al. Effects of paternal and maternal lifestyle factors on pregnancy complications and perinatal outcome. A population-based birth-cohort study: The GECKO Drenthe cohort. Hum. Reprod. 2014;29:824–34.
100. Smidts DP, Oosterlaan J. How common are symptoms of ADHD in typically developing preschoolers? A study on prevalence rates and prenatal/demographic risk factors. Cortex. 2007;43:710–7.
101. Kuppens SMI, Kooistra L, Wijnen HA, Crawford S, Vader HL, Hasaart THM, et al. Maternal thyroid function during gestation is related to breech presentation at term. Clin. Endocrinol. (Oxf). 2010;72:820–4.
102. Beijers C, Burger H, Verbeek T, Bockting CLH, Ormel J. Continued smoking and continued alcohol consumption during early pregnancy distinctively associated with personality. Addict. Behav. Elsevier Ltd; 2014;39:980–6.
103. Elliott EJ, Payne J, Morris A, Haan E, Bower C. Fetal alcohol syndrome: a prospective national surveillance study. Arch. Dis. Child. 2008;93:732–7.
104. Resendiz M, Chen Y, Öztürk NC, Zhou FC. Epigenetic medicine and fetal alcohol spectrum disorders Marisol. Epigenomics. 2013;5:73–86.
105. McBride N, Johnson S. Fathers' Role in Alcohol-Exposed Pregnancies. Systematic Review of Human Studies. Am. J. Prev. Med. Elsevier; 2016;1–9.
106. Dawson DA. Methodological issues in measuring alcohol use. Alcohol Res. Heal. 2003;27:18–29.
107. Sobell LC, Sobell MB. Alcohol consumption measures. Assess. alcohol Probl. A Guid. Clin. Res. 1995. p. 75–99.
108. Health Council of the Netherlands. Guidelines Healthy Nutrition. The Hague; 2015.

109. British Medical Association. Alcohol and pregnancy Preventing and managing fetal alcohol spectrum disorders. 2016.
110. May PA, Gossage JP. Maternal Risk Factors for Fetal Alcohol Spectrum Disorders: Not As Simple As It Might Seem. Alcohol Res. Heal. 2011;34:15–26.
111. Peters G-JY. A practical guide to effective behavior change: How to identify what to change in the first place. Eur. Heal. Psychol. 2014;16:142–55.
112. Kristjanson AF, Wilsnack SC, Zvartau E, Tsoy M, Novikov B. Alcohol use in pregnant and nonpregnant Russian women. Alcohol. Clin. Exp. Res. 2007;31:299–307.
113. Lee SH, Shin SJ, Won S-D, Kim E-J, Oh D-Y. Alcohol Use during Pregnancy and Related Risk Factors in Korea. Psychiatry Investig. 2010;7:86–92.
114. Balachova T, Bard D, Bonner B, Chaffin M, Isurina G, Tsvetkova L, et al. Do attitudes and knowledge predict at-risk drinking among Russian women? Am. J. Drug Alcohol Abuse. 2016;42:306–15.
115. Croxford, Julie, and Viljoen D. Alcohol consumption by pregnant women in the Western Cape. South African Med. J. 1999;89:962–5.
116. Peadon E, Payne J, Henley N, D'Antoine H, Bartu A, O'Leary C, et al. Attitudes and behaviour predict women's intention to drink alcohol during pregnancy: the challenge for health professionals. BMC Public Health. 2011;11:584.
117. Yamamoto Y, Kaneita Y, Yokoyama E, Sone T, Takemura S, Suzuki K, et al. Alcohol consumption and abstention among pregnant Japanese women. J Epidemiol. 2008;18:173–82.
118. van der Wulp NY, Hoving C, de Vries H. Partner's Influences and Other Correlates of Prenatal Alcohol Use. Matern. Child Health J. 2015;19:908–16.
119. McKnight A, Merrett D. Alcohol consumption in pregnancy—a health education problem. J. R. Coll. Gen. Pract. 1987;37:73–6.
120. Blume AWA, Resor MRM. Knowledge about health risks and drinking behavior among Hispanic women who are or have been of childbearing age. Addict. Behav. 2007;32:2335–9.
121. Kaminski M, Lelong N, Bean K, Chwalow J, Subtil D. Change in alcohol, tobacco and coffee consumption in pregnant women: evolution between 1988 and 1992 in an area of high consumption. Eur. J. Obstet. Gynecol. Reprod. Biol. 1995;60:121–8.
122. Kesmodel U, Schiøler Kesmodel P. Drinking during pregnancy: attitudes and knowledge among pregnant Danish women, 1998. Alcohol. Clin. Exp. Res. 2002;26:1553–60.
123. Leonardson GR, Loudenburg R, Struck J. Factors predictive of alcohol use during pregnancy in three rural states. Behav. brain Funct. 2007;3:8.
124. Lelong N, Kaminski M, Chwalow J, Bean K, Subtil D. Attitudes and behavior of pregnant women and health professionals towards alcohol and tobacco consumption. Patient Educ. Couns. 1995;25:39–49.
125. Kaskutas LA. Understanding Drinking During Pregnancy Among Urban American Indians and African Americans: Health Messages, Risk Beliefs, and How We Measure Consumption. Alcohol. Exp. Res. 2000;24:1241–50.
126. Pettigrew S, Jongenelis M, Chikritzhs T, Pratt IS, Slevin T, Glance D. A Comparison of Alcohol Consumption Intentions Among Pregnant Drinkers and Their Nonpregnant Peers of Child-Bearing Age. Subst. Use Misuse. 2016;6084:1–7.
127. Moore PJ, Turner R, Park CL, Adler NE. The impact of behavior and addiction on psychological models of cigarette and alcohol use during pregnancy. Addict. Behav. 1996;21:645–58.
128. Chang G, McNamara T, Wilkins-Haug L, Orav EJ. Stages of change and prenatal alcohol use. J. Subst. Abuse Treat. 2007;32:105–9.
129. Crawford-Williams F, Steen M, Esterman A, Fielder A, Mikocka-Walus A. "My midwife said that having a glass of red wine was actually better for the baby": a focus group study of women and their partner's knowledge and experiences relating to alcohol consumption in pregnancy. BMC Pregnancy Childbirth. 2015;15:79.
130. Watt MH, Eaton LA, Choi KW, Velloza J, Kalichman SC, Skinner D, et al. "It's better for me to drink, at least the stress is going away": Perspectives on alcohol use during pregnancy among South African women attending drinking establishments. Soc. Sci. Med. 2014;116:119–25.

131. World Health Organization. Global strategy to reduce the harmful use of alcohol. Geneva; 2010.
132. Sedgh G, Singh S, Hussain R. Intended and unintended pregnancies worldwide in 2012 and recent trends. Stud. Fam. Plann. 2014;45:301–14.
133. Babor TF, Jernigan D, Brookes C, editors. The Regulation of Alcohol Marketing: From Research to Public Health Policy. Addiction. 2017.
134. Kok G, Gottlieb NH, Panne R, Smerecnik C. Methods for environmental change; an exploratory study. BMC Public Health. BMC Public Health; 2012;12:1037.
135. Kok G, Gottlieb NH, Commers M, Smerecnik C. The Ecological Approach in Health Promotion Programs : A Decade Later. 2008;22:437–42.
136. Barbour BG. Alcohol and pregnancy. J. Nurse. Midwifery. 1990;35:78–85.
137. Van der Wulp NY, Hoving C, De Vries H. A qualitative investigation of alcohol use advice during pregnancy: experiences of Dutch midwives, pregnant women and their partners. Midwifery. Elsevier; 2013;29:e89-98.
138. Wechsler H, Nelson TF. What we have learned from the Harvard School of Public Health College Alcohol Study: Focusing attention on college student alcohol consumption and the environmental conditions that promote it. J. Stud. Alcohol Drugs. 2008;69:481–90.
139. Swan GE, Carmelli D, Rosenman RH, Fabsitz RR, Christian JC. Smoking and alcohol consumption in adult male twins: Genetic heritability and shared environmental influences. J. Subst. Abuse. 1990;2:39–50.
140. Kok G, Gurabardhi Z, Gottlieb NH, Zijlstra FRH. Influencing Organizations to Promote Health: Applying Stakeholder Theory. Heal. Educ. Behav. 2015;42:123S–132S.
141. Grol R, Wensing M, Eccles M, Davis D, editors. Improving patient care: the implementation of change in health care. John Wiley & Sons; 2013.
142. Bell, E., Andrew, G., Di Pietro, N., Chudley, A. E., Reynolds, J. N., & Racine E. It ' s a Shame ! Stigma Against Fetal Alcohol Spectrum Disorder : Examining the Ethical Implications for Public Health Practices and Policies. Public Health Ethics. 2016;9:65–77.
143. Racine E, Bell E, Zizzo N, Green C. Public discourse on the biology of alcohol addiction: Implications for stigma, self-control, essentialism, and coercive policies in pregnancy. Neuroethics. 2015;8:177–86.
144. Bos AER, Pryor JB, Reeder GD, Stutterheim SE. Stigma: Advances in Theory and Research. Basic Appl. Soc. Psych. 2013;35:1–9.
145. Dovidio JF, Major B, Crocker J. Stigma: Introduction and overview. In: Heatherton TF, Kleck RE, Hebl MR, Hull JG, editors. Soc. Psychol. stigma. New York, NY: Guilford Press; 2011. p. 1–28.
146. Pryor, J. B., & Reeder GD. HIV-related stigma. In: Hall JC, Hall BJ, Cockerell CJ, editors. HIV/AIDS Post-HAART Era Manifestations, Treat. Epidemiol. Shelton: CT: PMPH-USA; 2011. p. 790–806.
147. Davis JL, Manago B. Motherhood and associative moral stigma: The moral double bind. Stigma Heal. 2016;1:72–86.
148. Stutterheim SE, Baas I, Roberts H, Brands R, Schmidt J, Lechner L, et al. Stigma experiences among substance users with HIV. Stigma Heal. 2016;1.
149. Hammer R, Dingel M, Ostergren J, Partridge B, McCormick J, Koenig BA. Addiction: Current Criticism of the Brain Disease Paradigm. AJOB Neurosci. 2013;4:27–32.
150. Copeland B. Searching for, Finding and Experiencing Friendship: A Qualitative Study of Friendship Experiences of Seven Young Adults with Fetal Alcohol Syndrome/Effects. Victoria, BC.; 2002.
151. Dej E. What Once Was Sick is now Bad: The Shift from Victim to Deviant Identity for Those Diagnosed with Fetal Alcohol Spectrum Disorder. Can. J. Sociol. 2011;36:137–60.
152. Salmon J, Buetow S. An Exploration of the Experiences and Perspectives of New Zealanders with Fetal Alcohol Spectrum Disorder. J. Popul. Ther. Clin. Pharmacol. 2011;19:e41–50.
153. Shankar I. Risky Bodies: Allocation of Risk and Responsibility within Fetal Alcohol Spectrum Disorder (FASD) Prevention Campaigns. Can. Disabil. Stud. Assoc. 2016;5:152–77.
154. Wood M. Journeys of Birth Mothers of Children With FASD (Doctoral dissertation). 2010.
155. Salmon J. Fetal alcohol spectrum disorder: New Zealand birth mothers' experiences. Can. J. Clin. Pharmacol. 2008;15:e191-213.

156. Masood AF, Turner LA, Baxter A. Causal Attributions and Parental Attitudes Toward Children With Disabilities in the United States and Pakistan. 2007;73:475–87.
157. Stade B, Beyene J, Buller K, Ross S, Patterson K, Stevens B, et al. Feeling Different: The Experience of Living with Fetal Alcohol Spectrum Disorder. J. Popul. Ther. Clin. Pharmacol. 2010;18:e475–85.
158. Pereira R. Burden Experienced by Caregivers of Youth with Fetal Alcohol Spectrum Disorder: An Exploratory Study. University of Calgary Faculty; 2010.
159. Whitehurst T. Raising a child with foetal alcohol syndrome: Hearing the parent voice. Br. J. Learn. Disabil. 2012;40:187–93.
160. Bell E, Zizzo N, Racine E. Caution! Warning Labels About Alcohol and Pregnancy: Unintended Consequences and Questionable Effectiveness. Am. J. Bioeth. 2015;15:18–20.
161. Eggertson L. Stigma a major barrier to treatment for pregnant women with addictions. Can. Med. Assoc. J. 2013;185:1562.
162. Nelson M, Trussler M, editors. Fetal Alcohol Spectrum Disorder in Adults: Ethical and Legal Perspectives. New York: Springer International Publishing; 2016.
163. Children Act [Internet]. 1989. Available from: http://www.legislation.gov.uk/ukpga/1989/41/contents
164. Children Act [Internet]. UK Public General Act; 2004. Available from: http://www.legislation.gov.uk/ukpga/2004/31/contents
165. Allen A. Genetic Privacy: Emerging Concepts and Values. In: Rothstein M, editor. Genet. Secrets Prot. Priv. Confidentiality Genet. Era. Yale: Yale University Press; 1997. p. 31–60.
166. Medical Treatment Contracts Act - Wet geneeskundige behandelingsovereenkomst (WGBO). Article 7.457.
167. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, Official Journal L 281, 23/11/1995 P.0031-0050 [Internet]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML
168. Jane Roe v. Henry Wade. District Attorney of Dallas County 410 U.S. 113; 1973.
169. Larcher V, Brierley J. Fetal alcohol syndrome (FAS) and fetal alcohol spectrum disorder (FASD)—diagnosis and moral policing; an ethical dilemma for paediatricians. Arch. Disabil. Child. 2014;
170. Beauchamp T, Childress J. Principles of Biomedical Ethics (7th edition). Oxford: Oxford university Press; 2013.
171. Kok G, Bartholomew LK, Parcel GS, Gottlieb NH, Fernández ME. Finding theory- and evidence-based alternatives to fear appeals: Intervention Mapping. Int. J. Psychol. 2014;49:98–107.
172. Peters GJY, Ruiter RAC, Kok G. Threatening communication: a critical re-analysis and a revised meta-analytic test of fear appeal theory. Health Psychol. Rev. 2013;7:1–24.
173. Ruiter RAC, Kessels LTE, Peters GJY, Kok G. Sixty years of fear appeal research: current state of the evidence. Int. J. Psychol. 2014;49:63–70.
174. Kok G. A practical guide to effective behavior change How to apply theory- and evidence-based behavior change methods in an intervention. Eur. Heal. Psychol. 2014;16:156–70.
175. Skagerström J, Chang G, Nilsen P. Predictors of drinking during pregnancy: a systematic review. J Womens Heal. 2011;20:901–13.
176. Hastings G. “They’ll drink bucket loads of the stuff”: An analysis of internal alcohol industry advertising documents. London; 2009.
177. France KE, Donovan RJ, Bower C, Elliott EJ, Payne JM, D’Antoine H, et al. Messages that increase women’s intentions to abstain from alcohol during pregnancy: results from quantitative testing of advertising concepts. BMC Public Health. 2014;14:30.
178. Monteiro MG, Babor TF, Jernigan D, Brookes C. Alcohol marketing regulation : from research to public policy. Addiction. 2017;112:3–6.
179. Van der Wulp NY, Hoving C, Eijmael K, Candel MJ, van Dalen W, De Vries H. Reducing Alcohol Use During Pregnancy Via Health Counseling by Midwives and Internet-Based Computer-Tailored Feedback: A Cluster Randomized Trial. J. Med. Internet Res. 2014;16.

180. Negen Maanden Niet. Voorlichtingsprogramma voor de verloskundigenpraktijk over alcoholgebruik tijdens de zwangerschap. Ned. Inst. voor Alcoholbeleid. 2011.
181. Buunk AP, Van Vugt M. Applying social psychology: From problems to solutions. London: SAGE Publications; 2013.
182. Hoyme HE, Kalberg WO, Elliott AJ, Blankenship J, Buckley D, Marais A-S, et al. Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. Pediatrics. 2016;138:e20154256–e20154256.
183. Stratton K, Howe C, Battaglia FC (Eds.). Fetal alcohol syndrome: Diagnosis, epidemiology, prevention, and treatment. National Academies Press; 1996.
184. Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. Pediatrics. 2005;115:39–47.
185. Astley S., Clarren S. Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. Alcohol Alcohol. 2000;35:400–10.
186. Astley S. Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code. J. Popul. Ther. Clin. Pharmacol. 2013;20:e416-67.
187. Chudley AE, Conry J, Cook JL, Loock C, Rosales T, Leblanc N. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. Can. Med. Assoc. J. 2005;172:S1–21.
188. Cook JL, Green CR, Lilley CM, Anderson SM, Baldwin ME, Chudley AE, et al. Fetal alcohol spectrum disorder: a guideline for diagnosis across the lifespan. Can. Med. Assoc. J. 2016;188:191–7.
189. Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: an overview. Neuropsychol. Rev. 2011;21:73–80.
190. Coles CD, Gailey AR, Mulle JG, Kable JA, Lynch ME, Jones KL. A Comparison Among 5 Methods for the Clinical Diagnosis of Fetal Alcohol Spectrum Disorders. Alcohol. Clin. Exp. Res. 2016;n/a-n/a.
191. Hoyme HE, May P a, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. Pediatrics. 2005;115:39–47.
192. Mattson SN, Schoenfeld AM, Riley EP. Teratogenic effects of alcohol on brain and behavior. Alcohol Res. Heal. 2001;25:185–91.
193. Hellemans KG, Sliwowska JH, Verma P, Weinberg J. Prenatal alcohol exposure: fetal programming and later life vulnerability to stress, depression and anxiety disorders. Neurosci. Biobehav. Rev. 2010;34:791–807.
194. Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. Neuropsychol. Rev. 2011;21:81–101.
195. Doyle LR, Mattson SN. Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE): review of evidence and guidelines for assessment. Curr. Dev. Disord. reports. 2015;2:175–86.
196. Mattson SN, Riley EP, Gramling L, Delis DC, Jones KL. Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. J. Pediatr. 1997;131:718–21.
197. Testa M, Quigley BM, Eiden RD. The effects of prenatal alcohol exposure on infant mental development: a meta-analytical review. Alcohol Alcohol. 2003;38:295–304.
198. Rasmussen C, Horne K, Witol A. Neurobehavioral functioning in children with fetal alcohol spectrum disorder. Child Neuropsychol. 2006;12:453–68.
199. Wechsler D. Wechsler-Bellevue Intelligence Scale. New York: The Psychological Corporation; 1938.
200. Deary IJ, Strand S, Smith P, Fernandes C. Intelligence and educational achievement. Intelligence. 2007;35:13–21.
201. Gottfredson LS. The general intelligence factor. Sci. Am. 1998;24–9.
202. Hurks PPM, Hendriksen JGM, Dek JE, Kooij AP. Normal Variability of Children's Scaled Scores on Subtests of the Dutch Wechsler Preschool and Primary scale of Intelligence–Third Edition. Clin. Neuropsychol. 2013;27:988–1003.
203. Van Boxtel H, Hurks PPM. Intelligentiebepaling bij zeer lage niveaus. Tijdschr. voor Neuropsychol. 2012;7:40–8.

204. Watkins MW, Glutting JJ, Lei PW. Validity of the Full-Scale IQ when there is significant variability among WISC-III and WISC-IV factor scores. Appl. Neuropsychol. 2007;14:13–20.
205. Anderson P. Assessment and development of executive function (EF) during childhood. Child Neuropsychol. 2002;8:71–82.
206. Ware AL, Kulesz PA, Williams VJ, Juranek J, Cirino PT, F letcher JM. Gray matter integrity within regions of the dorsolateral prefrontal cortical-subcortical network predicts executive function and fine motor dexterity in spina bifida. Neuropsychology. 2016;30:492.
207. Sonuga-Barke E, Bitsakou P, Thompson M. Beyond the dual pathway model: evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry. 2010;49:345–55.
208. Ware AL, Infante MA, O'Brien JW, Tapert SF, Jones KL, Riley EP, et al. An fMRI study of behavioral response inhibition in adolescents with and without histories of heavy prenatal alcohol exposure. Behav. Brain Res. 2015;278:137–46.
209. Fuglestad AJ, Whitley ML, Carlson SM, Boys CJ, Eckerle JK, Fink BA, et al. Executive functioning deficits in preschool children with Fetal Alcohol Spectrum Disorders. Child Neuropsychol. 2015;21:716–31.
210. Rasmussen C, Bisanz J. Executive functioning in children with fetal alcohol spectrum disorders: profiles and age-related differences. Child Neuropsychol. 2009;15:201–15.
211. Kodituwakku PW, Kalberg W, May PA. The effects of prenatal alcohol exposure on executive functioning. Alcohol Res. Heal. 2001;25:192–8.
212. Coggins TE, Olswang LB, Carmichael Olson H, Timler GR. On becoming socially competent communicators: The challenge for children with fetal alcohol exposure. Int. Rev. Res. Ment. Retard. 2003;27:121–50.
213. Glass L, Graham DM, Akshoomoff N, Mattson SN. Cognitive factors contributing to spelling performance in children with prenatal alcohol exposure. Neuropsychology. 2015;29:817.
214. Kodituwakku PW, May PA, Clericuzio CL, Weers D. Emotion-related learning in individuals prenatally exposed to alcohol: an investigation of the relation between set shifting, extinction of responses, and behavior. Neuropsychologia. 2001;39:699–708.
215. Barkley RA, Edwards G, Laneri M, Fletcher K, Metevia L. Executive functioning, temporal discounting, and sense of time in adolescents with attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). J. Abnorm. Child Psychol. 2001;29:541–56.
216. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. J. child Psychol. psychiatry. 1996;37:51–87.
217. Reiter A, Tucha O, Lange KW. Executive functions in children with dyslexia. Dyslexia. 2005;11:116–31.
218. Geurts HM, Verté S, Oosterlaan J, Roeyers H, Sergeant JA. How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? J. child Psychol. psychiatry. 2004;45:836–54.
219. Watson SM, Westby CE, Gable RA. A framework for addressing the needs of students prenatally exposed to alcohol and other drugs. Prev. Sch. Fail. Altern. Educ. Child. Youth. 2007;52:25–32.
220. Zelazo PD, Carlson SM. Hot and cool executive function in childhood and adolescence: Development and plasticity. Child Dev. Perspect. 2012;6:354–60.
221. Bechara A. The role of emotion in decision-making: evidence from neurological patients with orbitofrontal damage. Brain Cogn. 2004;55:30–40.
222. Eslinger PJ, Flaherty-Craig, C. V., Benton AL. Developmental outcomes after early prefrontal cortex damage. Brain Cogn. 2004;55:84–103.
223. Yau WYW, Zubieta JK, Weiland BJ, Samudra PG, Zucker RA, Heitzeg MM. Nucleus accumbens response to incentive stimuli anticipation in children of alcoholics: relationships with precursive behavioral risk and lifetime alcohol use. J. Neurosci. 2012;32:2544–51.
224. Wass TS, Simmons RW, Thomas JD, Riley EP. Timing accuracy and variability in children with prenatal exposure to alcohol. Alcohol. Clin. Exp. Res. 2002;26:1887–96.
225. Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics. 2007;119:e733–41.

226. Evers A. The internationalization of test reviewing: Trends, differences, and results. Int. J. Test. 2012;12:136–56.
227. van Boxtel HW, Hemker BT. Weten¬schappelijke verantwoording van de Intelligentietest Eindtoets Basisonderwijs. Arnhem; 2009.
228. Hurks PP, Bakker H. Assessing intelligence in children and youth living in the Netherlands. J. Sch. Educ. Psychol. 2016;1–10.
229. Grigorenko EL, Sternberg RJ. Dynamic testing. Psychol. Bull. 1998;124:75.
230. Resing W, de Jong FM, Bosma T, Tunteler E. Learning during dynamic testing: Variability in strategy use by indigenous and ethnic minority children. J. Cogn. Educ. Psychol. 2009;8:22–37.
231. D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Rathouz PJ, Lahey BB. Causal inferences regarding prenatal alcohol exposure and childhood externalizing problems. Arch. Gen. Psychiatry. 2007;64:1296–304.
232. Fan J, Jacobson SW, Taylor PA, Molteno CD, Dodge NC, Stanton ME, et al. White matter deficits mediate effects of prenatal alcohol exposure on cognitive development in childhood. Hum. Brain Mapp. 2016;37:2943–2958.
233. Sood B, Delaney-Black, V., Covington, C., Nordstrom-Klee B, Ager J, Templin T, Janisse J, Martier S, et al. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. dose-response effect. Pediatrics. 2001;108:e34–e34.
234. Swaab H, Bouma A, Hendriksen J, König C. Klinische kinderneuropsychologie. Amsterdam: Boom Uitgevers; 2011.
235. Buck GH, Polloway EA, Kirkpatrick MA, Patton JR, Fad KM. Developing Behavioral Intervention Plans A Sequential Approach. Interv. Sch. Clin. 2000;36:3–9.
236. Nash K, Stevens S, Greenbaum R, Weiner J, Koren G, Rovet J. Improving executive functioning in children with fetal alcohol spectrum disorders. Child Neuropsychol. 2015;21:191–209.
237. Melby-Lervåg M, Redick TS, Hulme C. Working memory training does not improve performance on measures of intelligence or other measures of "far transfer" evidence from a meta-analytic review. Perspect. Psychol. Sci. 2016;11:512–34.
238. Norman AL, Crocker N, Mattson SN, Riley EP. Neuroimaging and fetal alcohol spectrum disorders. Dev. Disabil. Res. Rev. 2009;15:209–17.
239. Wang X, Kroenke CD. Utilization of Magnetic Resonance Imaging in Research Involving Animal Models of Fetal Alcohol Spectrum Disorders. Alcohol Res. 2015;37:39–51.
240. Moore EM, Migliorini R, Infante MA, Riley EP. Fetal Alcohol Spectrum Disorders: Recent Neuroimaging Findings. Curr. Dev. Disord. reports. 2014;1:161–72.
241. Wozniak JR, Muetzel RL. What does diffusion tensor imaging reveal about the brain and cognition in fetal alcohol spectrum disorders? Neuropsychol. Rev. 2011;21:133–47.
242. Rodrigues Pereira R, Rijpstra A. Jaarverslag NSCK 2008. Leiden; 2009.
243. Wieringen H Van, Letteboer TGW, Pereira RR, Ruiter S De, Balemans WAF, Lindhout D. Diagnostiek van foetale alcoholspectrumstoornissen. 2010;1–8.
244. Goh PK, Doyle LR, Glass L, Jones KL, Riley EP, Coles CD, et al. A Decision Tree to Identify Children Affected by Prenatal Alcohol Exposure. J. Pediatr. Elsevier Inc.; 2016;177:1–8.
245. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk Factors for Adverse Life Outcomes in Fetal Alcohol Syndrome and Fetal Alcohol Effects. Dev. Behav. Pediatr. 2004;25:228–329.
246. Mukherjee R, Cook PA, Fleming KM, Norgate SH. What can be done to lessen morbidity associated with fetal alcohol spectrum disorders? Arch. Dis. Child. 2016;archdischild-2016-310822.
247. Siderius EJ, Carmiggelt B, Rijn CS van, Heerkens YF. Preventive Child Health Care within the Framework of the Dutch Health Care System. J. Pediatr. [Internet]. Elsevier; 2016;177:S138–41. Available from: http://dx.doi.org/10.1016/j.jpeds.2016.04.050
248. Montag AC. Fetal alcohol-spectrum disorders: Identifying at-risk mothers. Int. J. Womens. Health. 2016;8:311–23.

249. Barr HM, Bookstein FL, O'Malley KD, Connor PD, Huggins JE, Streissguth AP. Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in Young Adult Offspring. Am. J. Psychiatry. 2006;163:1061–5.
250. ArgumentenFabriek., ZonMw. Knelpuntenanalyses jeugdgezondheidszorg [Internet]. 2013. Available from: http://www.zonmw.nl/nl/publicaties/detail/derde-knelpuntenanalyses-programma-richtlijnen-jeugdgezondheidszorg-2013-2018/?no_cache=1&cHash=522a18e34da50412bffc1f35182034e8
251. Popova S, Lange S, Burd L, Rehm J. Health care burden and cost associated with fetal alcohol syndrome: Based on official canadian data. PLoS One. 2012;7:2–8.
252. Popova S, Lange S, Burd L, Nam S, Rehm J. Special Education of Children with Fetal Alcohol Spectrum Disorder. Exceptionality,. 2016;24:165–75.
253. Popova, S., Lange, S., Burd, L., & Rehm J. Canadian Children and Youth in Care: The Cost of Fetal Alcohol Spectrum Disorder. Child Youth Care Forum. 2014;43:83–96.
254. Popova S, Lange S, Burd L, Urbanoski K, Rehm J. Cost of specialized addiction treatment of clients with fetal alcohol spectrum disorder in Canada. BMC Public Health. 2013;13:570.
255. Popova, S., Lange, S., Burd, L., & Rehm J. Cost attributable to Fetal Alcohol Spectrum Disorder in the Canadian correctional system. Int J Law Psychiatry. 2015;41:76–81.
256. Popova S, Lange S, Burd L, Rehm J. The Economic Burden of Fetal Alcohol Spectrum Disorder in Canada in 2013. Alcohol Alcohol. 2016;51:367–75.
257. Popova S, Lange S, Burd L, Shield K, Rehm J. Cost of speech-language interventions for children and youth with foetal alcohol spectrum disorder in Canada. Int. J. Speech. Lang. Pathol. 2014;16:571–81.
258. Thanh NX, Jonsson E. Costs of health services utilization of people with fetal alcohol spectrum disorder by sex and age group in Alberta, Canada. J Popul Ther Clin Pharmacol. 2014;21:e421-430.
259. Popova S, Lange S, Burd L, Chudley AE, Clarren SK, Rehm J. Cost of Fetal Alcohol Spectrum Disorder Diagnosis in Canada. PLoS One. 2013;8.
260. Ericson L, Magnusson L, Hovstadius B. Societal costs of fetal alcohol syndrome in Sweden. Eur. J. Heal. Econ. Springer Berlin Heidelberg; 2016;1–11.
261. Hopkins RB, Paradis J, Roshankar T, Bowen J, Tarride, J. E., Blackhouse, G., . . . Longo CJ. Universal or targeted screening for fetal alcohol exposure: a cost-effectiveness analysis. J Stud Alcohol Drugs. 2008;69:510–9.
262. Popova S, Lange S, Burd L, Urbanoski K, Rehm J. Cost of specialized addiction treatment of clients with fetal alcohol spectrum disorder in Canada. BMC Public Health. 2013;13:570.
263. Thanh NX, Jonsson E, Moffatt J, Dennett L, Chuck AW, Birchard S. An economic evaluation of the parent-child assistance program for preventing fetal alcohol spectrum disorder in Alberta, Canada. Adm Policy Ment Heal. 2015;42:10–8.
264. De Wit GA. Maatschappelijke kosten-baten analyse van beleidsmaatregelen om alcoholgebruik te verminderen. RIVM rapport 2016-0133. 2016;148.
265. European Union. 2014 Report on the State of the Art of Rare Disease Activities in Europe [Internet]. 2014. Available from: http://www.eucerd.eu/upload/file/Reports/2014ReportStateofArtRDActivitiesIT.pdf
266. Heus GCBB, Elzen APM Van Den, Brooks AS. Een syndroomdiagnose en dan? Tijdschr. Kindergeneeskd. 2014;82:49–52.
267. Petrenko CLM, Alto ME. Interventions in fetal alcohol spectrum disorders: An international perspective. Eur. J. Med. Genet. [Internet]. Elsevier Masson SAS; 2016;60:79–91. Available from: http://dx.doi.org/10.1016/j.ejmg.2016.10.005
268. Reid N, Dawe S, Shelton D, Harnett P, Warner J, Armstrong E, et al. Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol. Clin. Exp. Res. 2015;39:2283–95.

Appendices

LIST OF ABBREVIATIONS

ADH	Alcohol dehydrogenase
ADH1B	Alcohol Dehydrogenase 1B (Class I), Beta Polypeptide
ADH1C	Alcohol Dehydrogenase 1C (Class I), Gamma Polypeptide
ADHD	Attention-deficit/hyperactivity disorder
ALDH	Aldehyde dehydrogenases
ALDH2	Aldehyde dehydrogenase 2 family (Mitochondrial)
ATP	Adenosine triphosphate
ARBD	Alcohol-related birth defects
ARND	Alcohol-related neurodevelopmental disorders
BAC	Blood alcohol content or concentration
BMA	British Medical Association
CAT	Catalase
CDT	Carbohydrate-deficient transferrin
CNTN4	Contactin 4
CYHC	Child and Youth Health Care
CYP2E1	cytochrome P450 2E1
DHM	Dihydromyricetin
DNA	Deoxyribonucleic acid
EtOH	Ethanol
FAIR	Findable, Accessible, Interoperable, Reusable
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorders
FOXO	Forkhead box O
FSIQ	Full Scale Intelligence Quotient
GABA	Gamma-aminobutyric acid
GPX	Glutathione peroxidase
GWAS	Genome-wide association study
IOM	Institute of medicine
IM	Intervention Mapping
IQ	Intelligence quotient
KNOV	Royal Dutch organization of midwives
NOS	Newcastle-Ottawa Scale
NSCK	The Dutch Signaling Center for Pediatricians
NVOG	The national scientific association of gynecologists
PFAS	Partial fetal alcohol syndrome
PFC	Prefrontal cortex
PGM1	Phosphoglucomutase-1 gene
ROS	Radical oxygen species
SD	Standard deviation

SNPs	Single nucleotide polymorphisms
SOD	Superoxide dismutase
TAS2R	Taste 2 receptor
TAS2R38	Taste 2 receptor member 38
TF	Transferrin gene

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TABLE A1

Table A1 Study Characteristics of Maternal Alcohol Drinking Behaviors Related to FASD (Belonging to Paragraph 2.8)

Author (BibtexKey)	Geography	Sample year	Case	Control	Assessment methods	Maternal drinking behaviors & FASD Quotes	NOS score[2]
Cannon 2012	United States	1995-1997	353	3894874	record documentation	"Mothers of children with FAS have severe substance abuse behaviors including daily drinking, binge drinking"	4
Ceccanti 2014b	Italy	2014	39	108	interview	"Mothers of children with a FASD reported more drinking three months prior to pregnancy, more current drinking, and endorsed questionnaire items indicating that solitary drinking was more common"	9
Coyne 2008a	Australia	1994-2006	54	56	self-report	"Mothers of children with FAS reported heavy alcohol intake during pregnancy"	5
Davies 2011	South Africa	2002-2003	39	36	interview	"Twenty-five mothers with a FASD diagnosed child (69%) reported drinking alcohol, on average, every week during their pregnancy"	6
Leary 2010b	Australia	1995-1997			self-report	"Heavy PAE in the first trimester was associated with a more than fourfold increased risk of ARBDs. This association was specific to PAE in the first trimester. The finding of twofold increased odds of ARBDs after moderate levels of PAE during late pregnancy is likely because many women also had heavy first trimester exposure and reduced their alcohol intake as pregnancy progressed"	6
May 2000	South Africa		46	42	interview	"Most drinking is binge drinking. Even though the current drinking quantities reported by both subjects and controls were not high in absolute standards, the most important interpretation of the data is the large differential between subjects and controls. There is no doubt, however, that these mothers drank sufficiently to produce verifiable cases of fetal alcohol syndrome as severe as we have seen anywhere in the United States"	6

Author (BibtexKey)	Geography	Sample year	Case	Control	Assessment methods	Maternal drinking behaviors & FASD Quotes	NOS score[2]
May 2005	South Africa	1999-2001	53	116	interview	"Alcohol consumption was much greater for case mothers than for control mothers in all comparisons. Control mothers were more likely to have been abstainers or light drinkers compared with case mothers, who showed significantly heavier drinking patterns and reported drinking at the same level (53%-55%) or higher during pregnancy (32%-34%) compared with current drinking levels"	7
May 2007a	South Africa		61	133	interview	"Measures of drinking during the index pregnancies are significantly associated with low intelligence and frequent behavioral problems in the children. Reported drinking during pregnancy (.59), drinks per day (.48), three drinks or more per occasion (.51), and five drinks or more per occasion (.45), correlate highly with total dysmorphology in the children"	7
May 2008a	South Africa	2002	49 FAS, 15 pFAS	133	interview	"In most every variable of maternal alcohol use and abuse, a spectrum emerged based on the final diagnosis of the child with FAS, PFAS, and control. Alcohol use was greatest in quantity, frequency, and duration among the mothers of FAS children, and generally next most severe among mothers of PFAS children, while lowest among controls"	6
May 2011b	Italy	2011	8 FAS, 34 pFAS, 30 FASD	122	interview	"Mothers of children with FASD report heavy current drinking and drinking during the 2nd and 3rd trimesters of the index pregnancy"	9
May 2013d	South Africa	2013	63 FAS, 48 pFAS, 32 ARND	81	interview	"Binge drinking of at least two days a week during all trimesters in this population may produce FAS or PFAS, while mothers of children with ARND and exposed children without an FASD are most likely to reduce their average and peak alcohol consumption in the later trimesters"	7
May 2013e	South Africa	2013	68 FAS, 52 pFAS, 35 ARND	90	interview	"Mean number of drinks per week and drinking 3 and 5 or more drinks per occasion during pregnancy both illustrate the significant difference between mothers of FASD children and those of normal children"	7

Author (BibtexKey)	Geography	Sample year	Case	Control	Assessment methods	Maternal drinking behaviors & FASD Quotes	NOS score[2]
May 2014	United States	2010-2011	30	80	interview	"Mothers of children who had a FASD reported more drinking 3 months before pregnancy, and heavy drinking by the father of children who had FASD"	7
May 2014a	South Africa		43	85	interview	"With patterns of heavy episodic (binge) drinking being the most harmful to the fetus"	7
Miller 1995a	United States	1992-1994	22	214499	*unknown*	"Mothers of FAS cases were more likely to drink alcohol during pregnancy"	7
Petkovic 2013a	Croatia		55	769	self-report	"Confirmed pregnancy alcohol consumption in the FAS/PFAS group was higher (18.2%) to observed frequency in the whole sample of questioned mothers (11.5%) and significantly higher when compared to non-FAS/PFAS mothers (10.4%)"	7
Suttie 2013a	South Africa	2013	22 FAS, 26 pFAS	69	interview	"No differences were found for prenatal alcohol exposure between the HE subgroup with FAS/PFAS affinity (nonsyndromal heavy exposed with FAS/PFAS-like face signature [HE1]) versus the HE subgroup with control affinity (nonsyndromal heavy exposed with more control-like face signature [HE2]) (P < .10)"	5
Urban 2008	South Africa	2001-2004	82	74	interview	"Maternal drinking during pregnancy was much more frequently reported in mothers of children with FAS/PFAS than in controls"	6
Viljoen 2002a	South Africa	2001	31	31	interview	"Mothers of children with FAS drank significantly heavier than controls, especially for continues drinking heavily (and/or increasing) throughout pregnancy. Control mothers drank less and drinking levels declined during pregnancy. Episodic drinking on weekends was modal for both groups with bingeing 5+ drinks was normative during 2 constructive days for FAS mothers "	6
Viljoen 2005	South Africa	2005	53	116	interview	"Mothers of children with FAS drink more than controls, drink rapidly and drink heavily in an episodic fashion. Moreover, they do not quit or cut down during pregnancy"	7

note [1]measurements of maternal alcohol drinking behavior are categorized into three different levels: dichotomous (e.g., yes/no), nominal (e.g., admitted, negative, unanswered), ordinal (e.g., < 4 drinks, > 4 drinks), continuous (e.g., %). The measures represent the different questions asked for each category (e.g., "drank during the first trimester of pregnancy"). [2]Each study was assessed using the adapted version of The Newcastle – Ottawa Scale (NOS). Scores were allocated on a scale ranging from 0 (poor quality) to a maximum of 10 stars (excellent quality).

SEARCH QUERIES

Pathogenesis and Biomarkers

Search Query related to the origin of FASD and screening for alcohol consumption

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gestational alcohol exposure")
Pathogenesis	(mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* protein* OR metabol* OR transcript* OR biolog* OR biomarker* OR "oxidative stress")
Review	("systematic review" OR review OR meta*)

Ebscohost (CINAHL, PsychINFO, PsychARTICLES, MEDLINE)

("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gestational alcohol exposure") AND (mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* OR protein* OR metabol* OR transcript* OR biolog* OR biomarker* "oxidative stress") AND ("systematic review" OR review OR meta*)

PubMed Query Search

((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI]) OR (gestational alcohol exposure [TI])) AND ((mechanism* [TI]) OR (pathogen*[TI]) OR (pattern* [TI]) OR (system* [TI]) OR (gen* [TI]) OR (expression* [TI]) OR (protein* [TI]) OR (metabol* [TI]) OR (transcript*

[TI]) OR (biolog* [TI]) OR (biomarker* [TI]) OR (oxidative stress [TI])) AND ((systematic review [TI]) OR (review [TI]) OR (meta* [TI]))

(((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB]) OR (gestational alcohol exposure [TIAB])) AND ((mechanism* [TIAB]) OR (pathogen*[TIAB]) OR (pattern* [TIAB]) OR (system* [TIAB]) OR (gen* [TIAB]) OR (expression* [TIAB]) OR (protein* [TIAB]) OR (metabol* [TIAB]) OR (transcript* [TIAB]) OR (biolog* [TIAB]) OR (biomarker* [TIAB]) OR (oxidative stress [TIAB])) AND ((systematic review [TIAB]) OR (review [TIAB]) OR (meta* [TIAB]))

(((fetal alcohol spectrum disorder* [Text Word]) OR (foetal alcohol spectrum disorder* [Text Word]) OR (fetal alcohol exposure [Text Word]) OR (foetal alcohol exposure [Text Word]) OR (fetal alcohol syndrome [Text Word]) OR (foetal alcohol syndrome [Text Word]) OR (partial fetal alcohol syndrome [Text Word]) OR (partial fetal alcohol spectrum disorder* [Text Word]) OR (partial foetal alcohol syndrome [Text Word]) OR (partial foetal alcohol spectrum disorder* [Text Word]) OR (prenatal alcohol exposure [Text Word]) OR (prenatal exposure to alcohol [Text Word]) OR (alcohol exposed [Text Word]) OR (alcohol related birth defects [Text Word]) OR (alcohol related neurodevelopmental disorder [Text Word]) OR (fetal effects [Text Word]) OR (alcoholic embryopathy [Text Word]) OR (gestational alcohol exposure [Text Word])) AND ((mechanism* [Text Word]) OR (pathogen*[Text Word]) OR (pattern* [Text Word]) OR (system* [Text Word]) OR (gen* [Text Word]) OR (expression* [Text Word]) OR (protein* [Text Word]) OR (metabol* [Text Word]) OR (transcript* [Text Word]) OR (biolog* [Text Word]) OR (biomarker* [Text Word]) OR (oxidative stress [Text Word])) AND ((systematic review [Text Word]) OR (review [Text Word]) OR (meta* [Text Word]))

Embase (Ovid)

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gesta-

tional alcohol exposure") AND (mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* OR protein* OR metabol* OR transcript* OR biolog* OR biomarker* "oxidative stress") AND ("systematic review" OR review OR meta*)).ti.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gestational alcohol exposure") AND (mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* OR protein* OR metabol* OR transcript* OR biolog* OR biomarker* "oxidative stress") AND ("systematic review" OR review OR meta*)).ti.ab.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gestational alcohol exposure") AND (mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* OR protein* OR metabol* OR transcript* OR biolog* OR biomarker* "oxidative stress") AND ("systematic review" OR review OR meta*)).tw.

Note; If no reviews are available, use the queries below

Ebscohost (CINAHL, PsychINFO, PsychARTICLES, MEDLINE)

("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gestational alcohol exposure") AND (mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* OR protein* OR metabol* OR transcript* OR biolog* OR biomarker* "oxidative stress")

PubMed Query Search

((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI]) OR (gestational alcohol exposure [TI])) AND ((mechanism* [TI]) OR (pathogen*[TI]) OR (pattern* [TI]) OR (system* [TI]) OR (gen* [TI]) OR (expression* [TI]) OR (protein* [TI]) OR (metabol* [TI]) OR (transcript* [TI]) OR (biolog* [TI]) OR (biomarker* [TI]) OR (oxidative stress [TI]))

(((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB]) OR (gestational alcohol exposure [TIAB])) AND ((mechanism* [TIAB]) OR (pathogen*[TIAB]) OR (pattern* [TIAB]) OR (system* [TIAB]) OR (gen* [TIAB]) OR (expression* [TIAB]) OR (protein* [TIAB]) OR (metabol* [TIAB]) OR (transcript* [TIAB]) OR (biolog* [TIAB]) OR (biomarker* [TIAB]) OR (oxidative stress [TIAB]))

(((fetal alcohol spectrum disorder* [Text Word]) OR (foetal alcohol spectrum disorder* [Text Word]) OR (fetal alcohol exposure [Text Word]) OR (foetal alcohol exposure [Text Word]) OR (fetal alcohol syndrome [Text Word]) OR (foetal alcohol syndrome [Text Word]) OR (partial fetal alcohol syndrome [Text Word]) OR (partial fetal alcohol spectrum disorder* [Text Word]) OR (partial foetal alcohol syndrome [Text Word]) OR (partial foetal alcohol spectrum disorder* [Text Word]) OR (prenatal alcohol exposure [Text Word]) OR (prenatal exposure to alcohol [Text Word]) OR (alcohol exposed [Text Word]) OR (alcohol related birth defects [Text Word]) OR (alcohol related neurodevelopmental disorder [Text Word]) OR (fetal effects [Text Word]) OR (alcoholic embryopathy [Text Word]) OR (gestational alcohol exposure [Text Word])) AND ((mechanism* [Text Word]) OR (pathogen*[Text Word]) OR (pattern* [Text Word]) OR (system* [Text Word]) OR (gen* [Text Word]) OR (expression* [Text Word]) OR (protein* [Text Word]) OR (metabol* [Text Word]) OR (transcript* [Text Word]) OR (biolog* [Text Word]) OR (biomarker* [Text Word]) OR (oxidative stress [Text Word])) AND ((systematic review [Text Word])

Embase (Ovid)

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gestational alcohol exposure") AND (mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* OR protein* OR metabol* OR transcript* OR biolog* OR biomarker* "oxidative stress")).ti.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gestational alcohol exposure") AND (mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* OR protein* OR metabol* OR transcript* OR biolog* OR biomarker* "oxidative stress")).ti.ab.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy" OR "gestational alcohol exposure") AND (mechanism* OR pathogen* OR pattern* OR system* OR gen* OR expression* OR protein* OR metabol* OR transcript* OR biolog* OR biomarker* "oxidative stress")).tw.

Prevalence

Search Query related to FASD prevalence.

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Prevalence	("burden" OR "burden of disease" OR "prevalen*" OR "inciden*" OR "epidemiology" OR "epidemic*" OR “outcome*” OR “screening” OR “rate” OR “rating” OR “estimate” OR “experience”)
Review	("systematic review" OR review OR meta*)

EbscoHost (CINAHL, ERIC, PsychINFO, PsychARTICLES, MEDLINE) Query Search

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND ("burden" OR "burden of disease" OR "prevalen*" OR "inciden*" OR "epidemiology" OR "epidemic*" OR “outcome*” OR “screening” OR “rate” OR “rating” OR “estimate” OR “experience”) AND ("systematic review" OR review OR meta*))

PubMed Query Search

(((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI])) AND ((burden [TI]) OR (burden of disease [TI]) OR (prevalen* [TI]) OR (inciden* [TI]) OR (epidemiology [TI]) OR (epidemic* [TI]) OR (outcome* [TI]) OR (screening [TI]) OR (rate [TI]) OR (rating [TI]) OR (estimate [TI]) OR (experience [TI])) AND ((systematic review [TI]) OR (review [TI]) OR (meta* [TI]))

(((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB])) AND ((burden [TIAB]) OR (burden of disease [TIAB]) OR (prevalen* [TIAB]) OR (inciden* [TIAB]) OR (epidemiology [TIAB]) OR (epidemic* [TIAB]) OR (outcome* [TIAB]) OR (screening [TIAB]) OR (rate [TIAB]) OR (rating [TIAB]) OR (estimate [TIAB]) OR (experience [TIAB])) AND ((systematic review [TIAB]) OR (review [TIAB]) OR (meta* [TIAB]))

(((fetal alcohol spectrum disorder* [Text Word]) OR (foetal alcohol spectrum disorder* [Text Word]) OR (fetal alcohol exposure [Text Word]) OR (foetal alcohol exposure [Text Word]) OR (fetal alcohol syndrome [Text Word]) OR (foetal alcohol syndrome [Text Word]) OR (partial fetal alcohol syndrome [Text Word]) OR (partial fetal alcohol spectrum disorder* [Text Word]) OR (partial foetal alcohol syndrome [Text Word]) OR (partial foetal alcohol spectrum disorder* [Text Word]) OR (prenatal alcohol exposure [Text Word]) OR (prenatal exposure to alcohol [Text Word]) OR (alcohol exposed [Text Word]) OR (alcohol related birth defects [Text Word]) OR (alcohol related neurodevelopmental disorder [Text Word]) OR (fetal effects [Text Word]) OR (alcoholic embryopathy [Text Word])) AND ((burden [Text Word]) OR (burden of disease [Text Word]) OR (prevalen* [Text Word]) OR (inciden* [Text Word]) OR (epidemiology [Text Word]) OR (epidemic* [Text Word]) OR (outcome* [Text Word]) OR (screening [Text Word]) OR (rate [Text Word]) OR (rating [Text Word]) OR (estimate [Text Word]) OR (experience

[Text Word])) AND ((systematic review [Text Word]) OR (review [Text Word]) OR (meta* [Text Word])))

Embase Query Search

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND ("burden" OR "burden of disease" OR "prevalen*" OR "inciden*" OR "epidemiology" OR "epidemic*" OR "outcome*" OR "screening" OR "rate" OR "rating" OR "estimate" OR "experience") AND ("systematic review" OR review OR meta*)).ti.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND ("burden" OR "burden of disease" OR "prevalen*" OR "inciden*" OR "epidemiology" OR "epidemic*" OR "outcome*" OR "screening" OR "rate" OR "rating" OR "estimate" OR "experience") AND ("systematic review" OR review OR meta*)).ti.ab.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND ("burden" OR "burden of disease" OR "prevalen*" OR "inciden*" OR "epidemiology" OR "epidemic*" OR "outcome*" OR "screening" OR "rate" OR "rating" OR "estimate" OR "experience") AND ("systematic review" OR review OR meta*)).tw.

Behavior

Search Query related to maternal drinking behaviors.

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Pregnancy	(pregnan* OR gestat* OR maternal OR prenatal)
Behaviour	("alcohol use" OR "binge drinking" OR "alcohol abuse" OR "maternal drinking" OR "prenatal alcohol" OR "alcohol consumption" OR "alcohol drinking" OR "alcohol in utero" OR "maternal behav*" OR "ethanol teratogenesis" OR alcoholism OR "alcohol and pregnancy" OR "heavy drinking" OR "drinking during pregnancy" OR "behav* of mother*")
Correlate	(associat* OR correlat* OR predict* OR relat* OR caus* OR differ* OR determ* OR "risk factor")
Review	("systematic review" OR review OR meta*)
Exclude	(animal* OR drug* OR cocaine OR heroin)

Ebscohost

("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (pregnan* OR gestat* OR maternal OR prenatal) AND ("alcohol use" OR "binge drinking" OR "alcohol abuse" OR "maternal drinking" OR "prenatal alcohol" OR "alcohol consumption" OR "alcohol drinking" OR "alcohol in utero" OR "maternal behav*" OR "ethanol teratogenesis" OR alcoholism OR "alcohol and pregnancy" OR "heavy drinking" OR "drinking during pregnancy" OR "behav* of mother*")) AND (associat* OR correlat* OR predict* OR relat* OR caus* OR differ* OR determ* OR "risk factor") AND ("systematic review" OR review OR meta*) NOT (animal* OR drug* OR cocaine OR heroin))

PubMed Query Search

((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome[TI]) OR (partial fetal alcohol syndrome [TI])

OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI])) AND ((pregnan* [TI]) OR (gestat* [TI]) OR (maternal [TI]) OR (prenatal [TI])) AND ((alcohol use [TI]) OR (binge drinking [TI]) OR (alcohol abuse [TI]) OR (maternal drinking [TI]) OR (prenatal alcohol [TI]) OR (alcohol consumption [TI]) OR (alcohol drinking [TI]) OR (alcohol in utero [TI]) OR (maternal behav* [TI]) OR (ethanol teratogenesis [TI]) OR (alcoholism [TI]) OR (alcohol and pregnancy [TI]) OR (heavy drinking [TI]) OR (drinking during pregnancy [TI]) OR (behav* of mother* [TI])) AND ((associat* [TI]) OR (correlat* [TI]) OR (predict* [TI]) OR (relat* [TI]) OR (caus* [TI]) OR (differ* [TI]) OR (determ* [TI]) OR (risk factor [TI]) AND ((systematic review [TI]) OR (review [TI]) OR (meta* [TI])) NOT ((animal* [TI]) OR (drug* [TI]) OR (cocaine [TI]) OR (heroin [TI]))

((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome[TIAB]) OR (partial fetal alcohol syndrome[TIAB]) OR (partial fetal alcohol spectrum disorder*[TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder*[TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB])) AND ((pregnan* [TIAB]) OR (gestat* [TIAB]) OR (maternal [TIAB]) OR (prenatal [TIAB])) AND ((alcohol use [TIAB]) OR (binge drinking [TIAB]) OR (alcohol abuse [TIAB]) OR (maternal drinking [TIAB]) OR (prenatal alcohol [TIAB]) OR (alcohol consumption [TIAB]) OR (alcohol drinking [TIAB]) OR (alcohol in utero [TIAB]) OR (maternal behav* [TIAB]) OR (ethanol teratogenesis [TIAB]) OR (alcoholism [TIAB]) OR (alcohol and pregnancy [TIAB]) (heavy drinking [TIAB]) OR (drinking during pregnancy [TIAB]) OR (behav* of mother* [TIAB])) AND ((associat* [TIAB]) OR (correlat* [TIAB]) OR (predict* [TIAB]) OR (relat* [TIAB]) OR (caus* [TIAB]) OR (differ* [TIAB]) OR (determ* [TIAB]) OR (risk factor [TIAB]) AND ((systematic review [TIAB]) OR (review [TIAB]) OR (meta* [TIAB])) NOT ((animal* [TIAB]) OR (drug* [TIAB]) OR (cocaine [TIAB]) OR (heroin [TIAB]))

((fetal alcohol spectrum disorder* [TEXT WORD]) OR (foetal alcohol spectrum disorder* [TEXT WORD]) OR (fetal alcohol exposure [TEXT WORD]) OR (foetal alcohol exposure [TEXT WORD]) OR (fetal alcohol syndrome [TEXT WORD]) OR (foetal alcohol syndrome[TEXT WORD]) OR (partial fetal alcohol syndrome[TEXT WORD]) OR (partial fetal alcohol spectrum disorder*[TEXT WORD]) OR (partial foetal alcohol syndrome [TEXT WORD]) OR (partial foetal alcohol spectrum disorder*[TEXT WORD]) OR (prenatal alcohol exposure [TEXT WORD]) OR (prenatal exposure to alcohol [TEXT WORD]) OR (alcohol exposed [TEXT WORD]) OR (alcohol related birth defects [TEXT WORD])

OR (alcohol related neurodevelopmental disorder [TEXT WORD]) OR (fetal effects [TEXT WORD]) OR (alcoholic embryopathy [TEXT WORD])) AND ((pregnan* [TEXT WORD]) OR (gestat* [TEXT WORD]) OR (maternal [TEXT WORD]) OR (prenatal [TEXT WORD])) AND ((alcohol use [TEXT WORD]) OR (binge drinking [TEXT WORD]) OR (alcohol abuse [TEXT WORD]) OR (maternal drinking [TEXT WORD]) OR (prenatal alcohol [TEXT WORD]) OR (alcohol consumption [TEXT WORD]) OR (alcohol drinking [TEXT WORD]) OR (alcohol in utero [TEXT WORD]) OR (maternal behav* [TEXT WORD]) OR (ethanol teratogenesis [TEXT WORD]) OR (alcoholism [TEXT WORD]) OR (alcohol and pregnancy [TEXT WORD]) (heavy drinking [TEXT WORD]) OR (drinking during pregnancy [TEXT WORD]) OR (behav* of mother* [TEXT WORD])) AND ((associat* [TEXT WORD]) OR (correlat* [TEXT WORD]) OR (predict* [TEXT WORD]) OR (relat* [TEXT WORD]) OR (caus* [TEXT WORD]) OR (differ* [TEXT WORD]) OR (determ* [TEXT WORD]) OR (risk factor [TEXT WORD]) AND ((systematic review [TEXT WORD]) OR (review [TEXT WORD]) OR (meta* [TEXT WORD])) NOT ((animal* [TEXT WORD]) OR (drug* [TEXT WORD]) OR (cocaine [TEXT WORD]) OR (heroin [TEXT WORD]))

Embase Query Search

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (pregnan* OR gestat* OR maternal OR prenatal) AND ("alcohol use" OR "binge drinking" OR "alcohol abuse" OR "maternal drinking" OR "prenatal alcohol" OR "alcohol consumption" OR "alcohol drinking" OR "alcohol in utero" OR "maternal behav*" OR "ethanol teratogenesis" OR alcoholism OR "alcohol and pregnancy" OR "heavy drinking" OR "drinking during pregnancy" OR "behav* of mother*")) AND (associat* OR correlat* OR predict* OR relat* OR caus* OR differ* OR determ* OR "risk factor") AND ("systematic review" OR review OR meta*) NOT (animal* OR drug* OR cocaine OR heroin)).ti.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (pregnan* OR gestat* OR maternal OR prenatal) AND ("alcohol use" OR "binge drink-

ing" OR "alcohol abuse" OR "maternal drinking" OR "prenatal alcohol" OR "alcohol consumption" OR "alcohol drinking" OR "alcohol in utero" OR "maternal behav*" OR "ethanol teratogenesis" OR alcoholism OR "alcohol and pregnancy" OR "heavy drinking" OR "drinking during pregnancy" OR "behav* of mother*")) AND (associat* OR correlat* OR predict* OR relat* OR caus* OR differ* OR determ* OR "risk factor") AND ("systematic review" OR review OR meta*) NOT (animal* OR drug* OR cocaine OR heroin)).ti.ab.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (pregnan* OR gestat* OR maternal OR prenatal) AND ("alcohol use" OR "binge drinking" OR "alcohol abuse" OR "maternal drinking" OR "prenatal alcohol" OR "alcohol consumption" OR "alcohol drinking" OR "alcohol in utero" OR "maternal behav*" OR "ethanol teratogenesis" OR alcoholism OR "alcohol and pregnancy" OR "heavy drinking" OR "drinking during pregnancy" OR "behav* of mother*")) AND (associat* OR correlat* OR predict* OR relat* OR caus* OR differ* OR determ* OR "risk factor") AND ("systematic review" OR review OR meta*) NOT (animal* OR drug* OR cocaine OR heroin)).tw.

Determinants

Search Query related to determinants of maternal drinking behavior.

Keyword	Synonyms
Pregnancy	(pregnan* OR gestat* OR maternal OR prenatal OR antenatal)
Alcohol	(alcohol* OR drink* OR ethanol)
Determinant	(determin* OR intention* OR knowlegde OR risk perception OR reason* OR motiv* OR attitude* OR belief* OR outcome* OR expect* OR norm* OR self-efficacy OR perceived control OR perceived behav* control OR correlat* OR anteced* OR factor*)
Review	(systematic review OR review OR "meta*")
Exclude	(animal* OR mouse OR mice OR rat OR rats)

PsycINFO, PsycARTICLES, CINAHL, ERIC, MEDLINE

(("prenat*" OR "maternal" OR "prenatal" OR "antenatal" OR "gestat*") AND ("alcohol*" OR "drink*" OR "ethanol") AND ("determin*" OR "intention*" OR "knowlegde" OR "risk perception" OR "reason*" OR "motiv*" OR "attitude*" OR "belief*" OR "outcome*" OR "expect*" OR "norm*" OR "self-efficacy" OR "perceived control" OR "perceived behav* control" OR "correlat*" OR "anteced*" OR "factor*") AND ("systematic review" OR review OR meta*) NOT ("animal*" OR "mouse" OR "mice" OR "rat" OR "rats"))

PubMed

(((pregnan* [Text Word]) OR (maternal [Text Word]) OR (prenatal [Text Word]) OR (antenatal [Text Word]) OR (gestat* [Text Word])) AND ((alcohol* [Text Word]) OR (drink* [Text Word]) OR (ethanol [Text Word])) AND ((determin* [Text Word]) OR (intention* [Text Word]) OR (knowledge [Text Word]) OR (risk perception [Text Word]) OR (reason* [Text Word]) OR (motiv* [Text Word]) OR (attitude* [Text Word]) OR (belief* [Text Word]) OR (outcome* [Text Word]) OR (expect* [Text Word]) OR (norm [Text Word]) OR (norms [Text Word]) OR (normative [Text Word]) OR (self-efficacy [Text Word]) OR (perceived control [Text Word]) OR (perceived behav* control [Text Word]) OR (control belief* [Text Word]) OR (correlat* [Text Word]) OR (anteced* [Text Word]) OR (factor* [Text Word])) AND ((systematic review [TI]) OR (review [TI]) OR (meta* [TI])) NOT ((animal* [Text Word]) OR (mouse [Text Word]) OR (mice [Text Word]) OR (rat [Text Word]) OR (rats [Text Word])))

Stakeholders

Search Query related to stakeholders

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Pregnancy	(pregnan* OR gestat* OR maternal OR prenatal)
Stakeholders	(stakeholder* OR parent* OR individual* OR industry OR "healthcare professional*" OR researcher* OR "policy maker")
Review	("systematic review" OR review OR meta*)

Ebscohost

((("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")) OR ((pregnan* OR gestat* OR maternal OR prenatal)) AND (stakeholder* OR parent* OR individual* OR industry OR "healthcare professional*" OR researcher* OR "policy maker"))

Pubmed

(((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI])) OR ((pregnan* [TI]) OR (gestat* [TI]) OR (maternal [TI]) OR (prenatal [TI])) AND ((stakeholder* [TI]) OR (parent* [TI]) OR (individual* [TI]) OR (industry [TI]) OR (healthcare professional* [TI]) OR (researcher* [TI]) OR (policy maker [TI])))

(((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal

alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB])) OR ((pregnan* [TIAB]) OR (gestat* [TIAB]) OR (maternal [TIAB]) OR (prenatal [TIAB])) AND ((stakeholder* [TIAB]) OR (parent* [TIAB]) OR (individual* [TIAB]) OR (industry [TIAB]) OR (healthcare professional* [TIAB]) OR (researcher* [TIAB]) OR (policy maker [TIAB])))

(((fetal alcohol spectrum disorder* [TEXT WORD]) OR (foetal alcohol spectrum disorder* [TEXT WORD]) OR (fetal alcohol exposure [TEXT WORD]) OR (foetal alcohol exposure [TEXT WORD]) OR (fetal alcohol syndrome [TEXT WORD]) OR (foetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol spectrum disorder* [TEXT WORD]) OR (partial foetal alcohol syndrome [TEXT WORD]) OR (partial foetal alcohol spectrum disorder* [TEXT WORD]) OR (prenatal alcohol exposure [TEXT WORD]) OR (prenatal exposure to alcohol [TEXT WORD]) OR (alcohol exposed [TEXT WORD]) OR (alcohol related birth defects [TEXT WORD]) OR (alcohol related neurodevelopmental disorder [TEXT WORD]) OR (fetal effects [TEXT WORD]) OR (alcoholic embryopathy [TEXT WORD])) OR ((pregnan* [TEXT WORD]) OR (gestat* [TEXT WORD]) OR (maternal [TEXT WORD]) OR (prenatal [TEXT WORD])) AND ((stakeholder* [TEXT WORD]) OR (parent* [TEXT WORD]) OR (individual* [TEXT WORD]) OR (industry [TEXT WORD]) OR (healthcare professional* [TEXT WORD]) OR (researcher* [TEXT WORD]) OR (policy maker [TEXT WORD])))

Embase

((("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")) OR ((pregnan* OR gestat* OR maternal OR prenatal)) AND (stakeholder* OR parent* OR individual* OR industry OR "healthcare professional*" OR researcher* OR "policy maker")).ti.

((("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol

spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")) OR ((pregnan* OR gestat* OR maternal OR prenatal)) AND (stakeholder* OR parent* OR individual* OR industry OR "healthcare professional*" OR researcher* OR "policy maker")).ti.ab.

((("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")) OR ((pregnan* OR gestat* OR maternal OR prenatal)) AND (stakeholder* OR parent* OR individual* OR industry OR "healthcare professional*" OR researcher* OR "policy maker")).tw.

Preconception healthcare, midwifery, obstetrics, gynecology, and pediatrics

Search Query related to preconception healthcare, midwifery, obstetrics, gynecology, and pediatrics

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Midwivery, Gynaecology, Pediatry	midw* OR obstetric* OR gynaec* OR paediatric* OR pediatr*
Review	("systematic review" OR review OR meta*)

Search Query for review articles

Pubmed

(((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI])) AND ((midw* [TI] OR (obstetric* [TI]) OR (gynaec* [TI]) OR (paediatric* [TI]) OR pediatric* [TI]) AND ((systematic review [TI]) OR (review [TI]) OR (meta* [TI])))

(((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB])) AND ((midw* [TIAB] OR (obstetric* [TIAB]) OR (gynaec* [TIAB]) OR (paediatric* [TIAB]) OR pediatric* [TIAB])) AND ((systematic review [TIAB]) OR (review [TIAB]) OR (meta* [TABI])))

Search Query if there are no review articles available

(((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI])) AND ((midw* [TI] OR (obstetric* [TI]) OR (gynaec* [TI]) OR (paediatric* [TI]) OR pediatric* [TI])))

(((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB])) AND ((midw* [TIAB] OR (obstetric* [TIAB]) OR (gynaec* [TIAB]) OR (paediatric* [TIAB]) OR pediatric* [TIAB])))

Stigma

Search Query related to stigma and stereotyping aspects of FASD and drinking during pregnancy

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Pregnancy	(pregnan* OR gestat* OR maternal OR prenatal)
Behavior	(alcohol OR 'alcohol consumption' OR drink*)
Stigma	(determinant* OR attitude OR stigma OR stereotyp* OR prejudice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*)
Review	("systematic review" OR review OR meta*)

Ebscohost (CINAHL, ERIC, PsychARTICLES, PsychINFO, MEDLINE)

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") OR (pregnan* OR gestat* OR maternal OR prenatal)) AND (alcohol OR "alcohol consumption" OR drink*) AND (determinant* OR attitude OR stigma OR stereotyp* OR prejudice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*) AND ("systematic review" OR review OR meta*))

Ebscohost Query when <u>no review</u> articles are available

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") OR (pregnan* OR gestat* OR maternal OR prenatal)) AND (alcohol OR "alcohol consumption" OR drink*) AND (determinant* OR attitude OR stigma OR stereotyp* OR preju-

dice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*))

Pubmed

(((fetal alcohol spectrum disorder* [TI] OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI]) OR ((pregnan* [TI]) OR (gestat* [TI]) OR (maternal [TI]) OR (prenatal [TI])) AND ((alcohol [TI]) OR (alcohol consumption [TI]) OR (drink* [TI])) AND ((determinant* [TI]) OR (attitude [TI]) OR (stigma [TI]) OR (stereotyp* [TI]) OR (prejudice [TI]) OR (blame [TI]) OR (responsibility [TI]) OR (norm [TI]) OR (intent* [TI]) OR (belief* [TI]) OR (emotion* [TI]) OR (cognit* [TI]) OR (discrim* [TI]) AND (((systematic review [TI]) OR (review [TI]) OR (meta* [TI]))))

(((fetal alcohol spectrum disorder* [TIAB] OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB]) OR ((pregnan* [TIAB]) OR (gestat* [TIAB]) OR (maternal [TIAB]) OR (prenatal [TIAB])) AND ((alcohol [TIAB]) OR (alcohol consumption [TIAB]) OR (drink* [TIAB])) AND ((determinant* [TIAB]) OR (attitude [TIAB]) OR (stigma [TIAB]) OR (stereotyp* [TIAB]) OR (prejudice [TIAB]) OR (blame [TIAB]) OR (responsibility [TIAB]) OR (norm [TIAB]) OR (intent* [TIAB]) OR (belief* [TIAB]) OR (emotion* [TIAB]) OR (cognit* [TIAB]) OR (discrim* [TIAB]) AND (((systematic review [TIAB]) OR (review [TIAB]) OR (meta* [TIAB]))))

(((fetal alcohol spectrum disorder* [TEXT WORD] OR (foetal alcohol spectrum disorder* [TEXT WORD]) OR (fetal alcohol exposure [TEXT WORD]) OR (foetal alcohol exposure [TEXT WORD]) OR (fetal alcohol syndrome [TEXT WORD]) OR (foetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol spectrum disorder* [TEXT WORD]) OR (partial foetal alcohol syndrome [TEXT WORD]) OR (partial foetal alcohol spectrum disorder* [TEXT WORD]) OR (prenatal alcohol exposure [TEXT WORD]) OR (prenatal exposure to alcohol [TEXT WORD]) OR (alcohol exposed [TEXT WORD]) OR (alcohol related birth defects [TEXT WORD]) OR

(alcohol related neurodevelopmental disorder [TEXT WORD]) OR (fetal effects [TEXT WORD]) OR (alcoholic embryopathy [TEXT WORD]) OR ((pregnan* [TEXT WORD]) OR (gestat* [TEXT WORD]) OR (maternal [TEXT WORD]) OR (prenatal [TEXT WORD])) AND ((alcohol [TEXT WORD]) OR (alcohol consumption [TEXT WORD]) OR (drink* [TEXT WORD])) AND ((determinant* [TEXT WORD]) OR (attitude [TEXT WORD]) OR (stigma [TEXT WORD]) OR (stereotyp* [TEXT WORD]) OR (prejudice [TEXT WORD]) OR (blame [TEXT WORD]) OR (responsibility [TEXT WORD]) OR (norm [TEXT WORD]) OR (intent* [TEXT WORD]) OR (belief* [TEXT WORD]) OR (emotion* [TEXT WORD]) OR (cognit* [TEXT WORD]) OR (discrim* [TEXT WORD]) AND (((systematic review [TEXT WORD]) OR (review [TEXT WORD) OR (meta* [TEXT WORD])))

Pubmed Query when <u>no review</u> articles are available

(((fetal alcohol spectrum disorder* [TI] OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI]) OR ((pregnan* [TI]) OR (gestat* [TI]) OR (maternal [TI]) OR (prenatal [TI])) AND ((alcohol [TI]) OR (alcohol consumption [TI]) OR (drink* [TI])) AND ((determinant* [TI]) OR (attitude [TI]) OR (stigma [TI]) OR (stereotyp* [TI]) OR (prejudice [TI]) OR (blame [TI]) OR (responsibility [TI]) OR (norm [TI]) OR (intent* [TI]) OR (belief* [TI]) OR (emotion* [TI]) OR (cognit* [TI]) OR (discrim* [TI])))

(((fetal alcohol spectrum disorder* [TIAB] OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB]) OR ((pregnan* [TIAB]) OR (gestat* [TIAB]) OR (maternal [TIAB]) OR (prenatal [TIAB])) AND ((alcohol [TIAB]) OR (alcohol consumption [TIAB]) OR (drink* [TIAB])) AND ((determinant* [TIAB]) OR (attitude [TIAB]) OR (stigma [TIAB]) OR (stereotyp* [TIAB]) OR (prejudice [TIAB]) OR (blame [TIAB]) OR (responsibility [TIAB]) OR (norm [TIAB]) OR (intent* [TIAB]) OR (belief* [TIAB]) OR (emotion* [TIAB]) OR (cognit* [TIAB]) OR (discrim* [TIAB])))

(((fetal alcohol spectrum disorder* [TEXT WORD] OR (foetal alcohol spectrum disorder* [TEXT WORD]) OR (fetal alcohol exposure [TEXT WORD]) OR (foetal alcohol exposure [TEXT WORD]) OR (fetal alcohol syndrome [TEXT WORD]) OR (foetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol spectrum disorder* [TEXT WORD]) OR (partial foetal alcohol syndrome [TEXT WORD]) OR (partial foetal alcohol spectrum disorder* [TEXT WORD]) OR (prenatal alcohol exposure [TEXT WORD]) OR (prenatal exposure to alcohol [TEXT WORD]) OR (alcohol exposed [TEXT WORD]) OR (alcohol related birth defects [TEXT WORD]) OR (alcohol related neurodevelopmental disorder [TEXT WORD]) OR (fetal effects [TEXT WORD]) OR (alcoholic embryopathy [TEXT WORD]) OR ((pregnan* [TEXT WORD]) OR (gestat* [TEXT WORD]) OR (maternal [TEXT WORD]) OR (prenatal [TEXT WORD])) AND ((alcohol [TEXT WORD]) OR (alcohol consumption [TEXT WORD]) OR (drink* [TEXT WORD])) AND ((determinant* [TEXT WORD]) OR (attitude [TEXT WORD]) OR (stigma [TEXT WORD]) OR (stereotyp* [TEXT WORD]) OR (prejudice [TEXT WORD]) OR (blame [TEXT WORD]) OR (responsibility [TEXT WORD]) OR (norm [TEXT WORD]) OR (intent* [TEXT WORD]) OR (belief* [TEXT WORD]) OR (emotion* [TEXT WORD]) OR (cognit* [TEXT WORD]) OR (discrim* [TEXT WORD])))

Embase (Ovid)

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") OR (pregnan* OR gestat* OR maternal OR prenatal) AND (alcohol OR "alcohol consumption" OR drink*) AND (determinant* OR attitude OR stigma OR stereotyp* OR prejudice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*) AND ("systematic review" OR review OR meta*)).ti.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") OR (pregnan* OR gestat* OR maternal OR prenatal) AND (alcohol OR "alcohol consumption" OR drink*) AND (determinant* OR attitude OR stigma OR stereotyp* OR preju-

dice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*) AND ("systematic review" OR review OR meta*)).ti.ab.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") OR (pregnan* OR gestat* OR maternal OR prenatal) AND (alcohol OR "alcohol consumption" OR drink*) AND (determinant* OR attitude OR stigma OR stereotyp* OR prejudice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*) AND ("systematic review" OR review OR meta*)).tw.

Embase Query when <u>no review</u> articles are available

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") OR (pregnan* OR gestat* OR maternal OR prenatal) AND (alcohol OR "alcohol consumption" OR drink*) AND (determinant* OR attitude OR stigma OR stereotyp* OR prejudice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*)).ti.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") OR (pregnan* OR gestat* OR maternal OR prenatal) AND (alcohol OR "alcohol consumption" OR drink*) AND (determinant* OR attitude OR stigma OR stereotyp* OR prejudice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*)).ti.ab.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foe-

tal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") OR (pregnan* OR gestat* OR maternal OR prenatal) AND (alcohol OR "alcohol consumption" OR drink*) AND (determinant* OR attitude OR stigma OR stereotyp* OR prejudice OR blame OR responsibility OR norm OR intent* OR belief* OR emotion* OR cognit* OR discrim*)).tw.

Ethics, Law

Search Query related to ethical and legal issues

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Pregnancy	(pregnan* OR gestat* OR maternal OR prenatal OR fetus OR "unborn child")
Normative	(ethic* OR law OR regulation* OR rule* OR "acceptable behav*" OR ought OR moral* OR responsibility OR duty OR right* OR autonomy OR "future child" OR "rights of unborn child" OR "right to choose" OR "negligence" OR criminal* OR stigma OR privacy)
Review	("systematic review" OR review OR meta*)

HeinOnline

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (pregnan* OR gestat* OR maternal OR prenatal OR fetus OR "unborn child") AND (ethic* OR law OR regulation* OR rule* OR "acceptable behav*" OR ought OR moral* OR responsibility OR duty OR right* OR autonomy OR "future child" OR "rights of unborn child" OR "right to choose" OR "negligence" OR criminal* OR stigma OR privacy) AND ("systematic review" OR review OR meta*))

Neuropsychological and behavioral effects

Search Query related to FASD neuropsychological characteristics

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Neurodevelopment	(neuro* OR brain* OR neural* OR cogn* OR pathway* OR process* OR productivit* OR fluenc* OR pattern* OR behav* OR structural OR motiv*)
Review	("systematic review" OR review OR meta*)

Ebscohost (CINAHL, ERIC, PsychARTICLES, PsychINFO, MEDLINE):

("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (neuro* OR brain* OR neural* OR cogn* OR pathway* OR process* OR productivit* OR fluenc* OR pattern* OR behav* OR structural OR motiv*) AND ("systematic review" OR review OR meta*)

Neuroimaging

Search Query related to FASD neuroimaging

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Neuroimaging	(neuroimag* OR neuroanat* OR brain* OR "Magnetic resonance imaging" OR FMRI OR "Diffusion tensor imaging" OR DTI OR MRS)
Review	("systematic review" OR review OR meta*)

Ebscohost

("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (neuroimag* OR neuroanat* OR brain* OR "Magnetic resonance imaging" OR FMRI OR "Diffusion tensor imaging" OR DTI OR MRS) AND ("systematic review" OR review OR meta*)

PubMed Query Search

((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI])) AND ((neuroimag* [TI]) OR (neuroanat* [TI]) OR (brain* [TI]) OR (Magnetic resonance imaging [TI]) OR (FMRI [TI]) OR (diffusion tensor imaging [TI]) OR (DTI [TI]) OR (MRS [TI])) AND ((systematic review [TI]) OR (review [TI]) OR (meta* [TI])))

Diagnostics

Search Query related to FASD diagnostics

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Diagnosis	(diagn* OR guideline OR protocol OR rule OR proced* OR instruct* OR standard*)
Review	("systematic review" OR review OR meta*)

Ebscohost

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (diagn* OR guideline OR protocol OR rule OR proced* OR instruct* OR standard*) AND ("systematic review" OR review OR meta*))

Pubmed

((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI])) AND ((diagn* [TI]) OR (guideline [TI]) OR (protocol [TI]) OR (rule [TI]) OR (proced* [TI]) OR (instruct* [TI]) OR (standard* [TI])) AND ((systematic review [TI]) OR (review [TI]) OR (meta* [TI]))

((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR

(prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB])) AND ((diagn* [TIAB]) OR (guideline [TIAB]) OR (protocol [TIAB]) OR (rule [TIAB]) OR (proced* [TIAB]) OR (instruct* [TIAB]) OR (standard* [TIAB])) AND ((systematic review [TIAB]) OR (review [TIAB]) OR (meta* [TIAB]))

((fetal alcohol spectrum disorder* [TEXT WORD]) OR (foetal alcohol spectrum disorder* [TEXT WORD]) OR (fetal alcohol exposure [TEXT WORD]) OR (foetal alcohol exposure [TEXT WORD]) OR (fetal alcohol syndrome [TEXT WORD]) OR (foetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol spectrum disorder* [TEXT WORD]) OR (partial foetal alcohol syndrome [TEXT WORD]) OR (partial foetal alcohol spectrum disorder* [TEXT WORD]) OR (prenatal alcohol exposure [TEXT WORD]) OR (prenatal exposure to alcohol [TEXT WORD]) OR (alcohol exposed [TEXT WORD]) OR (alcohol related birth defects [TEXT WORD]) OR (alcohol related neurodevelopmental disorder [TEXT WORD]) OR (fetal effects [TEXT WORD]) OR (alcoholic embryopathy [TEXT WORD])) AND ((diagn* [TEXT WORD]) OR (guideline [TEXT WORD]) OR (protocol [TEXT WORD]) OR (rule [TEXT WORD]) OR (proced* [TEXT WORD]) OR (instruct* [TEXT WORD]) OR (standard* [TEXT WORD])) AND ((systematic review [TEXT WORD]) OR (review [TEXT WORD]) OR (meta* [TEXT WORD]))

Embase

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (diagn* OR guideline OR protocol OR rule OR proced* OR instruct* OR standard*) AND ("systematic review" OR review OR meta*)).ti.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (di-

agn* OR guideline OR protocol OR rule OR proced* OR instruct* OR standard*) AND ("systematic review" OR review OR meta*)).ti.ab.

(("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy") AND (diagn* OR guideline OR protocol OR rule OR proced* OR instruct* OR standard*) AND ("systematic review" OR review OR meta*)).tw.

Prevention / Intervention

Search Query related to prevention and intervention of FASD/ prenatal alcohol exposure

Keyword	Synonyms
FASD	("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")
Pregnancy	(pregnan* OR gestat* OR maternal OR prenatal)
Prevention Intervention	(preven* OR interve* OR strategy OR education OR "health promot*" OR program*)
Review	("systematic review" OR review OR meta*)
Exclude	(animal* OR mouse OR mice OR rat OR rats)

Ebscohost

((("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")) OR ((pregnan* OR gestat* OR maternal OR prenatal)) AND (preven* OR interve* OR strategy OR education OR "health promot*" OR program*) AND ("systematic review" OR review OR meta*) NOT (animal* OR mouse OR mice OR rat*))

Pubmed

(((fetal alcohol spectrum disorder* [TI]) OR (foetal alcohol spectrum disorder* [TI]) OR (fetal alcohol exposure [TI]) OR (foetal alcohol exposure [TI]) OR (fetal alcohol syndrome [TI]) OR (foetal alcohol syndrome [TI]) OR (partial fetal alcohol syndrome [TI]) OR (partial fetal alcohol spectrum disorder* [TI]) OR (partial foetal alcohol syndrome [TI]) OR (partial foetal alcohol spectrum disorder* [TI]) OR (prenatal alcohol exposure [TI]) OR (prenatal exposure to alcohol [TI]) OR (alcohol exposed [TI]) OR (alcohol related birth defects [TI]) OR (alcohol related neurodevelopmental disorder [TI]) OR (fetal effects [TI]) OR (alcoholic embryopathy [TI])) OR ((pregnan* [TI]) OR (gestat* [TI]) OR (maternal [TI]) OR (prenatal [TI])) AND ((preven* [TI]) OR (interve* [TI]) OR (strategy [TI]) OR (education [TI]) OR (health promot* [TI]) OR (program* [TI])) AND ((systematic

review [TI]) OR (review [TI]) OR (meta* [TI])) NOT ((animal* [TI]) OR (mouse [TI]) OR (mice [TI]) OR (rat* [TI])))

(((fetal alcohol spectrum disorder* [TIAB]) OR (foetal alcohol spectrum disorder* [TIAB]) OR (fetal alcohol exposure [TIAB]) OR (foetal alcohol exposure [TIAB]) OR (fetal alcohol syndrome [TIAB]) OR (foetal alcohol syndrome [TIAB]) OR (partial fetal alcohol syndrome [TIAB]) OR (partial fetal alcohol spectrum disorder* [TIAB]) OR (partial foetal alcohol syndrome [TIAB]) OR (partial foetal alcohol spectrum disorder* [TIAB]) OR (prenatal alcohol exposure [TIAB]) OR (prenatal exposure to alcohol [TIAB]) OR (alcohol exposed [TIAB]) OR (alcohol related birth defects [TIAB]) OR (alcohol related neurodevelopmental disorder [TIAB]) OR (fetal effects [TIAB]) OR (alcoholic embryopathy [TIAB])) OR ((pregnan* [TIAB]) OR (gestat* [TIAB]) OR (maternal [TIAB]) OR (prenatal [TIAB])) AND ((preven* [TIAB]) OR (interve* [TIAB]) OR (strategy [TIAB]) OR (education [TIAB]) OR (health promot* [TIAB]) OR (program* [TIAB])) AND ((systematic review [TIAB]) OR (review [TIAB]) OR (meta* [TIAB])) NOT ((animal* [TIAB]) OR (mouse [TIAB]) OR (mice [TIAB]) OR (rat* [TIAB])))

(((fetal alcohol spectrum disorder* [TEXT WORD]) OR (foetal alcohol spectrum disorder* [TEXT WORD]) OR (fetal alcohol exposure [TEXT WORD]) OR (foetal alcohol exposure [TEXT WORD]) OR (fetal alcohol syndrome [TEXT WORD]) OR (foetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol syndrome [TEXT WORD]) OR (partial fetal alcohol spectrum disorder* [TEXT WORD]) OR (partial foetal alcohol syndrome [TEXT WORD]) OR (partial foetal alcohol spectrum disorder* [TEXT WORD]) OR (prenatal alcohol exposure [TEXT WORD]) OR (prenatal exposure to alcohol [TEXT WORD]) OR (alcohol exposed [TEXT WORD]) OR (alcohol related birth defects [TEXT WORD]) OR (alcohol related neurodevelopmental disorder [TEXT WORD]) OR (fetal effects [TEXT WORD]) OR (alcoholic embryopathy [TEXT WORD])) OR ((pregnan* [TEXT WORD]) OR (gestat* [TEXT WORD]) OR (maternal [TEXT WORD]) OR (prenatal [TEXT WORD])) AND ((preven* [TEXT WORD]) OR (interve* [TEXT WORD]) OR (strategy [TEXT WORD]) OR (education [TEXT WORD]) OR (health promot* [TEXT WORD]) OR (program* [TEXT WORD])) AND ((systematic review [TEXT WORD]) OR (review [TEXT WORD]) OR (meta* [TEXT WORD])) NOT ((animal* [TEXT WORD]) OR (mouse [TEXT WORD]) OR (mice [TEXT WORD]) OR (rat* [TEXT WORD])))

Embase

((("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neu-

rodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")) OR ((pregnan* OR gestat* OR maternal OR prenatal)) AND (preven* OR interve* OR strategy OR education OR "health promot*" OR program*) AND ("systematic review" OR review OR meta*) NOT (animal* OR mouse OR mice OR rat*)).ti.

((("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")) OR ((pregnan* OR gestat* OR maternal OR prenatal)) AND (preven* OR interve* OR strategy OR education OR "health promot*" OR program*) AND ("systematic review" OR review OR meta*) NOT (animal* OR mouse OR mice OR rat*)).ti.ab.

((("fetal alcohol spectrum disorder*" OR "foetal alcohol spectrum disorder*" OR "fetal alcohol exposure" OR "foetal alcohol exposure" OR "fetal alcohol syndrome" OR "foetal alcohol syndrome" OR "partial fetal alcohol syndrome" OR "partial fetal alcohol spectrum disorder*" OR "partial foetal alcohol syndrome" OR "partial foetal alcohol spectrum disorder*" OR "prenatal alcohol exposure" OR "prenatal exposure to alcohol" OR "alcohol exposed" OR "alcohol related birth defects" OR "alcohol related neurodevelopmental disorder" OR "fetal effects" OR "alcoholic embryopathy")) OR ((pregnan* OR gestat* OR maternal OR prenatal)) AND (preven* OR interve* OR strategy OR education OR "health promot*" OR program*) AND ("systematic review" OR review OR meta*) NOT (animal* OR mouse OR mice OR rat*)).tw.