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Understanding, predicting, and treating depression in pregnancy to improve mothers' and offspring's mental health outcomes: The HappyMums study

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ABSTRACT

Background: Perinatal depression is common: on average, more than 13% of women suffer from physician-diagnosed disorder and 20% report symptoms bearing clinical relevance. Maternal depression not only significantly impacts women's quality of life but also increases the offspring's risk of negative developmental outcomes, including mental disorders, through a combination of maternal alterations in *in-utero* biology and postnatal rearing factors during the early period of life. The HappyMums project aims to improve our understanding of perinatal depression by identifying the factors that robustly predict risk and resilience in mothers and their offspring, determining underlying neurobiological mechanisms, and, finally, testing the efficacy of potential interventions.

Methods: HappyMums will use data from a large collection of cohorts and registries containing biological, clinical, socio-demographic, environmental, and lifestyle data. It will pool unique human samples of maternal blood, placenta, chorionic villi and amniotic fluid, analyzing these data alongside pre-clinical samples of brain, blood and placental tissue from models of prenatal stress in mice and livebearing fish for correlative analyses. HappyMums will develop a mobile application (App) to collect multiple data types from women for early screening and monitoring of depressive symptoms.

Conclusion: The findings generated by HappyMums will be clinically relevant as they will increase the knowledge on perinatal depression, with unprecedented benefits for the offspring and the society as a whole.

1. Introduction

1.1. Background

Mental health conditions during the perinatal period, defined as the temporal window from pregnancy to 12 months after delivery, contribute enormously to societal and health burdens. Perinatal mental illness not only can have a long-term significant impact on the woman and family's well-being but is also associated with a huge economic cost for the society, estimated to be € 90.000 per affected woman; specifically perinatal depression alone accounts for € 75.000 per affected woman (Bauer et al., 2014, 2016). Importantly, more than three-quarters of this cost (72%) refers to the negative long-term impact of the illness on the child (Bauer et al., 2014). According to the World Health Organization (WHO),[1] depression is the most common mental health condition during the perinatal period, affecting about 10–13% of women in developed countries and about 20% of women in developing countries. Furthermore, even higher rates of antenatal and postnatal depression and anxiety have been reported during the COVID-19 pandemic compared to historical norms (Iyengar et al., 2021).

Women experiencing depression during pregnancy are often not identified (Biaggi et al., 2016). They fail to receive timely treatment because they may be unaware of their condition, or because they do not disclose their symptoms to healthcare professionals, for example, due to fear of perceived stigma (Byatt et al., 2013), difficulties accessing clinics or affording treatment. If they seek help, they might not find appropriate services, either due to difficulty accessing mental health services, especially in disadvantaged sociocultural settings (Munodawafa et al., 2018), or because depressive symptoms are often unrecognized by health professionals. This can lead to a persistence or exacerbation of symptoms in the postpartum period: indeed, antenatal depression represents one of the most significant risk factors for postnatal depression (Milgrom et al., 2008).

There is evidence that several clinical, psychosocial, and environmental factors as well as alterations in biological systems, such as in inflammation and the neuroendocrine system, are associated with the onset and progression of depression during the perinatal period (Angelotta and Wisner, 2017; Biaggi et al., 2016; Lin et al., 2019; Norhayati et al., 2015; Serati et al., 2016). However, we currently lack studies that i) integrate all these multimodal heterogeneous factors at a specific individual level, ii) include the potential role of protective factors and iii) test the role of placenta, of inflammation and neuroendocrine markers, genetics and epigenetics as possible overall mediators.

Perinatal depression not only affects a substantial proportion of women but also increases the risk of negative outcomes in the offspring, including a spectrum of cognitive and behavioural disturbances and mental health conditions (Rogers et al., 2020), through a combination of biological effects *in-utero* and psychosocial effects during the first years of life (Stein et al., 2014). Research has shown the involvement of multiple biological systems, including epigenetic regulation, hypothalamic-pituitary-adrenal (HPA) axis reactivity and brain structure and function (Cao-Lei et al., 2020; Koss and Gunnar, 2018; Suarez et al., 2018; Zou et al., 2019). In particular, alterations in the neuronal-immune-hormonal triad, that have been associated with antenatal depression (Serati et al., 2016), may affect the intrauterine environment, resulting in a species-atypical *in-utero* environment, affecting foetal development and shaping their risk of psychopathology later in life (Kreitz et al., 2020). Indeed, about 40–50% of offspring exposed to maternal perinatal depression develop less optimal emotional, behavioural or cognitive outcomes during childhood or adolescence (Hay et al., 2008; Lahti et al., 2017; Tuovinen et al., 2021). However, a similar proportion of children exposed to maternal depression do not develop such negative outcomes, thus remaining resilient. Although studies have shown that multiple pre- and postnatal factors are involved and can buffer or exacerbate the effects of maternal perinatal depression on offspring outcomes, the specific factors involved remain unidentified. In particular, we are currently lacking i) large-scale, integrative, and prospective data to map the relationship between maternal perinatal depression and offspring developmental outcomes and identify biological alterations occurring in utero; ii) large-scale epigenetic and neuroimaging longitudinal studies to trace postnatal developmental trajectories and establish their potential role in linking maternal perinatal depression to offspring outcomes; iii) multi-factorial analyses to identify genetic as well as pre- and postnatal factors modifying the effect of maternal depression on child outcomes, and to elucidate pathways characterizing vulnerable *vs* resilient offspring.

Therefore, it is of high importance to identify early on, with adequate

[1] Abbreviations: AI: Artificial Intelligence; CBT, Cognitive Behavioural Therapy; CDSS, Clinical Decision Support System; COVID-19, Coronavirus Disease of 2019; cRCT, Cluster-Randomized Clinical Trial; DNAm, DNA Methylation; DTI, Diffusion Tensor Imaging; ELS, Early-life-stress; GWAS, Genome-wide association studies; HPA axis, Hypothalamic-pituitary-adrenal axis; LBN, Limited bedding and nesting; MRI, Magnetic Resonance Imaging; MSUS, Unpredictable Maternal Separation Combined with Unpredictable Maternal Stress; NICE, National Institute for Health and Care Excellence; PNS, Prenatal Stress; RNASeq, RNA Sequencing; SIR, Chronic Social Isolation Rearing; WHO, World Health Organization.

programs of screening and monitoring, those women who are most at risk of perinatal depression and those already experiencing depressive symptoms, to then be able to provide interventions where necessary. Currently, in many countries, women at high risk of depression are often inadequately monitored during the perinatal period and limited tools, able to integrate different heterogeneous variables, are available for early monitoring of symptoms and self-help. The use of technology could facilitate this process, due to the possibility of reaching a large number of women and directly involving them in monitoring their mental health, promoting empowerment and reducing stigma. Although several applications (Apps) in mental health exist, also in the context of pregnancy (Hussain-Shamsy et al., 2020), currently, no Apps are routinely used by health professionals to monitor women's mental health during the perinatal period and none are able to integrate different sets of heterogeneous data.

Once women are identified as suffering from perinatal depression, treatment provided in a timely manner is crucial, to protect the well-being of both women and their babies. Both pharmacological and non-pharmacological interventions can improve clinical symptoms (Born et al., 2006). However, a clear understanding of how they influence the overall biology is still lacking. Furthermore, there is a compelling need to investigate how these interventions might exert an impact on offspring neurodevelopment and to identify putative biological mechanisms underlying this effect.

The incorporation of multiple study designs and models can indeed allow us to have a more comprehensive picture of perinatal depression Animal models can complement clinical and epidemiological studies and provide useful insights in understanding the underlying biological mechanisms. Exposure to sub-chronic- or chronic stressors during pregnancy in animals is frequently used to model the effects of prenatal stress as a proxy for human perinatal depression (Weinstock, 2017). However, most of the available models rely on the application of stress paradigms during specific phases of pregnancy, but this may be insufficient to model the complexity of antenatal depression. There is indeed still a lack of knowledge regarding the biological mechanisms underlying such behavioural alterations, and the role of the foetal environment, particularly the placenta in mediating the development of a pathological phenotype in the exposed offspring.

The objective of this paper is to present the HappyMums project, a large-scale interdisciplinary research programme that aims to improve our understanding of perinatal depression. The study will focus on both clinical depression (i.e., an episode of Major Depressive Disorder (MDD)) as well as on depressive symptoms, even if these do not meet diagnostic criteria, to maximize the opportunity for early detection and intervention. The project uses the biopsychosocial model of depression, which focuses on different aspects of the biological, psychological, and social perspective (Garcia-Toro and Aguirre, 2007) and combines both human and animal data. The project also brings together longitudinal data from large population-based birth cohorts, case-control studies during the perinatal period and clinical registers and integrates genetic, biological, environmental, lifestyle and demographic factors in mothers and offspring.

1.2. Overview of the HappyMums project and objectives

HappyMums is supported by the Horizon research and innovation programme (Grant n. 101,057,390) and brings together the expertise of 17 complimentary academic, industrial, clinical institutions and patients' associations across Europe and the United States. The project has been designed to investigate the risk and protective factors for perinatal depression and the underlying biological mechanisms. The project also aims to study the effects of perinatal depression on the offspring, shaping their risk for developing negative developmental outcomes later in life as well as the role of potentialmoderating of pre- and postnatal factors, including sex-specific trajectories. Finally, the project aims to evaluate the efficacy and the preventive potential of pharmacological and non-pharmacological interventions and understand their underlying mechanisms.

The project will also include the development of a smartphone App, that could be used by pregnant women to monitor their mental health. The App will require the direct involvement of the women, will be at the interface with clinicians and will collect multiple data modalities (e.g., biological, clinical, medical, environmental, and lifestyle data), for early detection and monitoring of depressive symptoms in pregnancy.

In particular, the HappyMums project has five main objectives.

1. Identify risk and protective factors for the development of depressive symptoms during the perinatal period and the associated biological blood signatures.
2. Understand the impact of maternal perinatal depressive symptoms on offspring developmental outcomes and identify underlying biological mechanisms as well as pre- and postnatal moderators.
3. Use animal models (mice and fish) to identify peripheral and brain molecular mal-adaptations associated with depressive symptoms during gestation and dissect the role of the placenta in mediating negative developmental outcomes in offspring.
4. Develop an innovative digital platform for an App-based early screening and monitoring of maternal depressive symptoms in pregnancy.
5. Integrate human and animal data to test novel interventions to prevent or improve depressive symptoms during pregnancy and to dissect the underlying biological mechanisms in mothers and the foetal environment.

2. Methodology

The aims of the HappyMums project will be achieved by focusing on different key points that represent the backbone of the project. Specifically, the project will develop five main concepts (Fig. 1).

- *Concept 1.* Multimodal predictors for depressive symptoms, their progression, and response to interventions.
- *Concept 2.* Biological signatures and markers linking maternal depressive symptoms to offspring outcomes and assessment of the role of postnatal factors as moderators.
- *Concept 3.* Neurobiological mechanisms and peripheral biomarkers using preclinical mouse and fish models.
- *Concept 4.* Personalized strategies to improve mental health in pregnant women using machine learning approaches and digital tools.
- *Concept 5.* Effects of pharmacological and non-pharmacological interventions in pregnancy and underlying biology.

In the following paragraphs, a detailed description of the methodology that will be used to develop each concept is provided.

2.1. Concept 1 - multimodal predictors for depressive symptoms, their progression, and response to interventions

Concept 1 aims to investigate predictors or moderators for the development of perinatal depression in women, by pooling large-scale, longitudinal, and deeply phenotyped data from existing population-based birth cohorts, case-control studies during the perinatal period, paediatric studies and clinical registers.

Factors investigated will include socio-demographic factors (e.g., age, maternal and paternal socio-economic status, education), medical factors (e.g., presence of other pathologies), clinical factors (e.g., history of depression or childhood trauma, sleep quality, presence of recent stressful events, reproductive history), environmental and lifestyle factors (e.g., smoking and/or substance abuse during pregnancy, presence of major life events, physical activity, diet) and biological factors (e.g., genetics, epigenetics, inflammation, metabolism-related biomarkers/

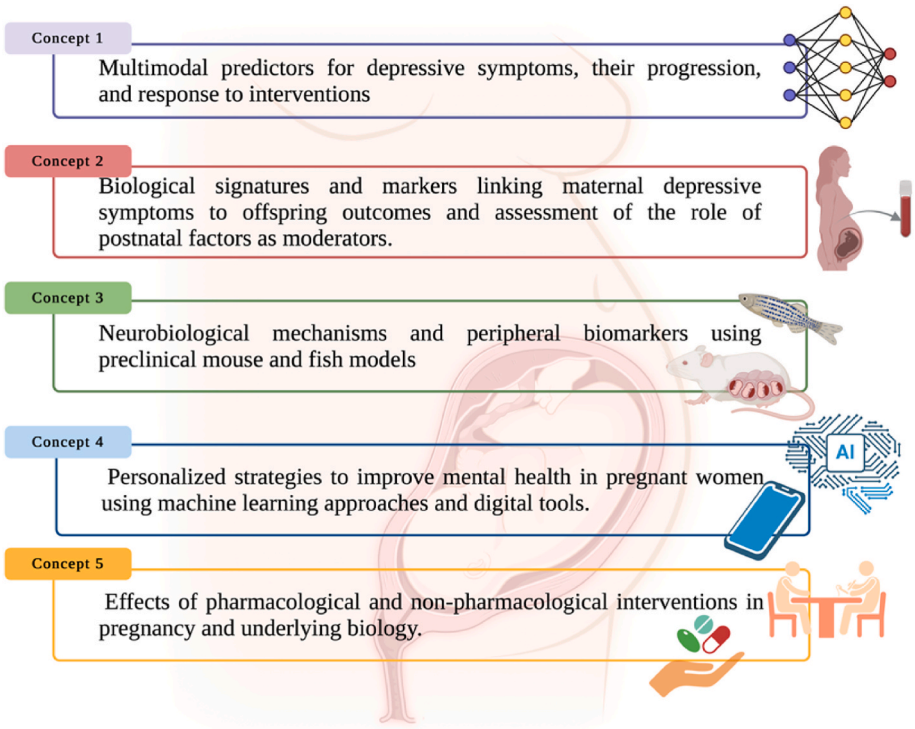

Fig. 1. The different Concepts within the HappyMums Study
The HappyMums project will develop five different concepts. Concept 1 will aim to identify multimodal predictors for depressive symptoms, their progression, and response to interventions. Concept 2 will aim to identify the biological signatures and markers linking maternal depressive symptoms to offspring outcomes together with the assessment of the role of postnatal factors as moderators. Concept 3 will take advantage of preclinical mouse and fish models to investigate the neurobiological mechanisms and peripheral biomarkers. Concept 4 will focus on personalized strategies to improve mental health in pregnant women using machine learning approaches and digital tools. Lastly, Concept 5 will investigate the effects of pharmacological and non-pharmacological interventions in pregnancy and the underlying biological mechanisms.

metabolites, and neuroendocrine-related biomarkers).

These factors will be analysed to identify those most robustly associated with the development of perinatal depressive symptoms by using different approaches, including a meta-analytical approach. A literature-based meta-analysis investigating factors associated with response to interventions for depression in pregnancy will also be conducted. Lastly, data will be integrated thanks to machine learning techniques, to map the predictive signatures for perinatal depression, identifying protective pathways, mediators, and moderators, as well as potential vulnerable or resilient sub-populations of women.

2.2. Concept 2 – biological signatures and markers linking maternal depressive symptoms to offspring outcomes and assessment of the role of postnatal factors as moderators

Concept 2 aims to understand the effects of perinatal depression on offspring development, identify biological signatures and markers linking maternal depressive symptoms to offspring outcomes, and assess the role of pre- and postnatal factors as moderators as well as potential mediators (Fig. 2). This will be done by pooling data from prospective epidemiological birth cohorts and paediatric studies as for Concept 1, bringing together thousands of children and their parents from different countries.

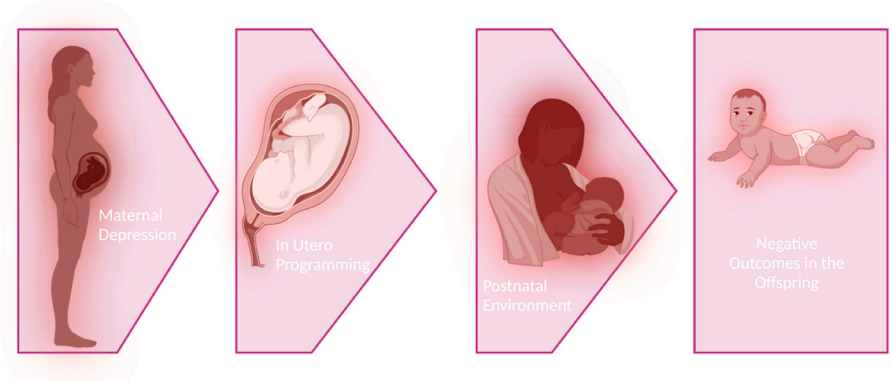

Fig. 2. The biology of perinatal depression and the consequences on the exposed offspring
The project aims to investigate how perinatal depression affects not only the mental health of the mothers but also the intrauterine environment and biology, negatively impacting the developing foetus and shaping the offspring's risk for the development of psychopathology later in life.

This concept will first test the associations of maternal perinatal depressive symptoms with offspring outcomes. In particular, the project will focus on multiple domains of functioning across developmental stages, including cognitive, neurodevelopmental, and psychiatric outcomes. The availability of repeated measures in subsamples of cohorts will allow for testing of the existence of distinct longitudinal profiles of maternal depressive symptoms (e.g., differing in onset, severity or chronicity) using clustering methods, and to assess whether these differentially associate with offspring outcomes.

Secondly, this concept aims to identify *in-utero* biological factors associated with exposure to maternal depressive symptoms in pregnancy and negative outcomes in the offspring. The project will bring together unique samples of amniotic fluid, chorionic villi, placenta, and cord blood as well as already generated omics data (GWAS, RNASeq, DNAm, metabolomics). Based on these data, possible associations between maternal depressive symptoms and biological alterations in the foetal environment will be investigated, focusing on the first trimester (chorionic villi) and term placenta functionality as well as amniotic fluid composition in terms of neuroendocrine, inflammatory, and metabolic markers. The project will also leverage on unique longitudinal epigenetic (DNAm) and neuroimaging (MRI, DTI) data in offspring across development (up to five time points from birth to adolescence), to examine neurobiological trajectories associated with exposure to perinatal depression, and their potential role in mediating effects on offspring outcomes.

Within this concept, the project also aims to identify the genetic, environmental, demographic and lifestyle factors that act as moderators or mediators of perinatal symptoms exposure on offspring mental health outcomes. For genetics, state-of-the-art analysis methods will be used to test if the offspring's genomic risk for depression and other disorders may moderate the relationship between maternal depressive symptoms and offspring outcomes. The availability of genetic data in both parents and offspring will also enable to disentangle potential routes of transmission linking perinatal depression to child outcomes, including separating direct genetic effects from genetic nurture effects. Environmental factors (e.g., stress exposure, parenting, peer relationships/social support and neighbourhood quality), lifestyle factors (e.g., diet, exercise, sleep) and medical factors (e.g., substance/medication use) will also be evaluated.

Lastly, data from both mothers and offspring will be integrated to map developmental pathways, mediators and moderators of offspring outcomes following exposure to maternal perinatal depressive symptoms, as well as to identify vulnerable and resilient signatures for negative outcomes thanks to techniques of data integration and machine learning procedures.

2.3. *Concept 3 – Neurobiological mechanisms and peripheral biomarkers using preclinical models*

Concept 3 aims to identify and validate neurobiological and peripheral biomarkers by using preclinical models. Specifically, three different but complementary rodent models (Fig. 3) will be used to incorporate distinct etiological risk factors of maternal depression during pregnancy.

1. The unpredictable maternal separation combined with unpredictable maternal stress (MSUS) paradigm, to provide a model of preconception depression in females, with symptoms of depressive-like states that persist throughout life (Weiss et al., 2011).
2. The chronic social isolation rearing (SIR) paradigm, to mimic a condition of continuous depressive-like state before and throughout gestation (Scarborough et al., 2021).
3. The prenatal stress followed by postnatal stress (PNS/LBN) paradigm, to mimic a depression-like state that develops during gestation and persists into the early postpartum period.

Dams exposed to SIR and PNS/LBN paradigm and pregnant female offspring from MSUS dams will be assessed for the development of behavioural alterations as well as for associated brain neuroanatomical (using *ex vivo* structural MRI and DTI) and molecular features. Male and female offspring will be behaviourally assessed at different postnatal ages (adolescence and adulthood) to stratify offspring into vulnerable and resilient subgroups, which will then be investigated for differences in brain neuroanatomy, structural connectivity, and molecular

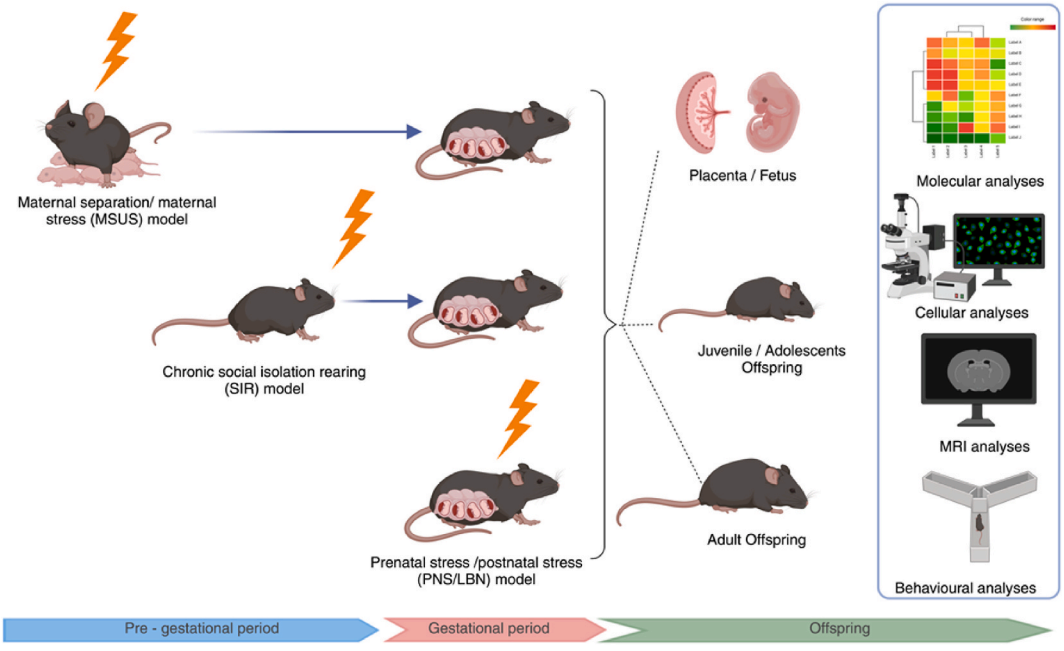

Fig. 3. Graphical representation of the Concept 3 experimental paradigm of the three rodent models
In the HappyMums project, three complementary rodent models will be included that incorporate distinct aetiological risk factors of maternal depression. These three models will allow a longitudinal postnatal assessment of behavioural functions in offspring as well as molecular signature in blood and brain in relation to the behavioural outcome.

alterations (RNAseq and DNAm analyses). As an overall strategy, *ex vivo* structural MRI and DTI will be acquired first to guide the selection of the brain regions to be investigated in terms of molecular mechanisms, networks and circuits affected by the gestational-perinatal manipulations (Mueller et al., 2021) (Fig. 3).

Moreover, analyses of the foetal environment, specifically amniotic fluid composition and molecular features in the placenta will allow us to assess how the depressive-like condition in pregnancy influences the foetal environment and offspring developmental trajectories. In particular, amniotic fluid composition will be tested by using metabolomic analyses to get information on inflammatory and neuroendocrine markers. The placenta transcriptome and DNA methylome will be investigated by RNAseq and DNAm analyses to identify biological alterations (by RNAseq) and evaluate if these alterations are associated with changes in epigenetic regulation (by DNAm).

Finally, concept 3 also aims to dissect the role of the placenta by using an innovative fish model represented by fishes of the family Poeciliidae, where the placenta evolved multiple times (Furness et al., 2019; Pollux et al., 2009; van Kruistum et al., 2021). This family represents a unique system to study placenta composition, because it contains closely related live-bearing species that lack placentas or have highly complex placentas (Pollux et al., 2014; Safian et al., 2023), and these fishes lack post-natal maternal care (Furness et al., 2019). To specifically dissect the role of the placenta in mediating the effect of exposure to depressive-like behaviour in pregnancy on negative outcomes in the offspring, behavioural and molecular analyses (RNAseq, DNAm) will be conducted both in mothers and in their offspring (Fig. 4).

2.4. Concept 4 - Personalized strategies to improve mental health in pregnant women using machine learning approaches and digital tools

Concept 4 aims to develop personalized strategies to improve mental health in pregnant women by using machine learning approaches and digital tools. In this context, concept 4 will develop i) a digital platform and ii) a large-scale testing study to prove the validity of such a platform.

The digital platform (Fig. 5) will be developed in the early phases of the project and will be composed of:

1. HappyMums App for pregnant women for screening, risk detection and symptom monitoring
2. HappyMums clinical dashboard for clinicians for clinical data collection and patient monitoring

The HappyMums App will collect different sets of data (clinical features, medical and biological features, social features, cognitive data, physical data, voice and speech and facial expressions). These data will be collected in multiple ways: by manual data entry (e.g., completing questionnaires and periodically reporting medical and biological data), active interaction with the system (e.g., voice analysis and facial expressions, execution of game-like exercises), and passive monitoring (e.g., background collection of data coming from smartphone embedded sensors, such as physical and social activity). Besides collecting the information, the App will contain a reminders-based module to support its uptake and use. The App will also include a *Mum-to-be mental well-being* course, developed by mental health professionals of the HappyMums project, to provide information on mental well-being during pregnancy.

The App will require the direct involvement of the women, therefore contributing to reducing stigma by empowering mothers to monitor and master their mental health (Fig. 6). To this end, the App will include recommendations to promote mental health during pregnancy. These will include, for example, advice regarding healthier lifestyle habits that will be identified as protective factors for women's mental health, reducing the risk of developing depressive symptoms.

In terms of the HappyMums online dashboard, it will include a comprehensive visual display for assessing women's condition, according to data collected through the developed mobile health tool (e.g., periodic mental health tests or smartphone sensor data). A visual analytics framework will be further utilized to present knowledge to health professionals in an optimal way, via visual annotations, plots and graphs, data comparison charts and cluster-based visualizations.

Once the App is developed, a large-scale testing study will be implemented to prove the validity of the platform. The study will be performed across different clinical centres in Europe (7 centres across 6 countries: Italy (2), Germany, UK, Poland, Croatia and Finland). Each of the involved centres will recruit 150 pregnant women considered at risk of antenatal depression or already suffering from depressive symptoms (total N = 1000). Risk for antenatal depression will be established using a screening questionnaire where women will be asked about multiple risk factors for antenatal depression previously identified within the literature. A subset of at least 210 women (30 women per site) will then be included in a testing study to prove the validity of the platform. The

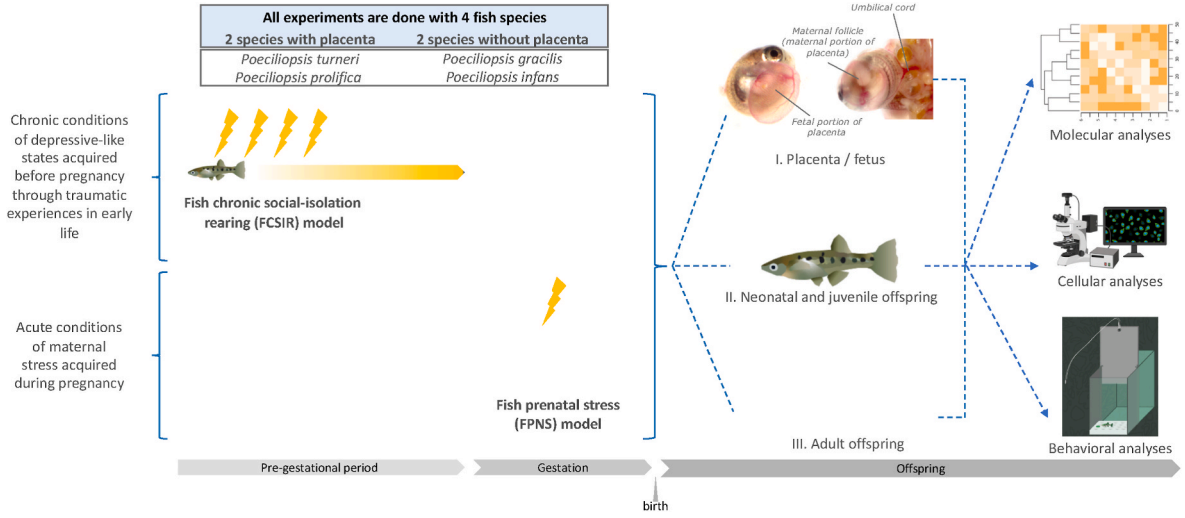

Fig. 4. Graphical representation of the Concept 3 experimental paradigm of the novel live-bearing fish models
In the HappyMums project, four closely related live-bearing fish species from the family Poeciliidae will be included, of which two have a placenta and two lack a placenta. These fish models will allow comparisons between closely related livebearing species with and without placentas to elucidate specifically the role and mechanisms of the placenta in transferring the adverse effects of maternal depression during pregnancy to the developing offspring in utero.

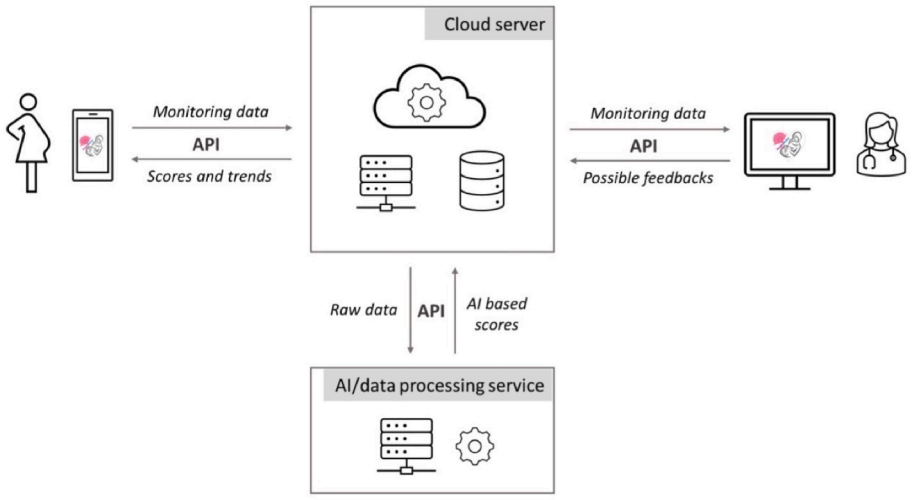

Fig. 5. HappyMums platform components and interactions
The HappyMums digital platform is composed of: A) an App for pregnant women meant for screening risk detection and symptoms monitoring; B) a clinical dashboard for clinical data collection and patient monitoring; this platform backend will run on a cloud-based infrastructure that will manage data storage, data processing and data exchange between components.

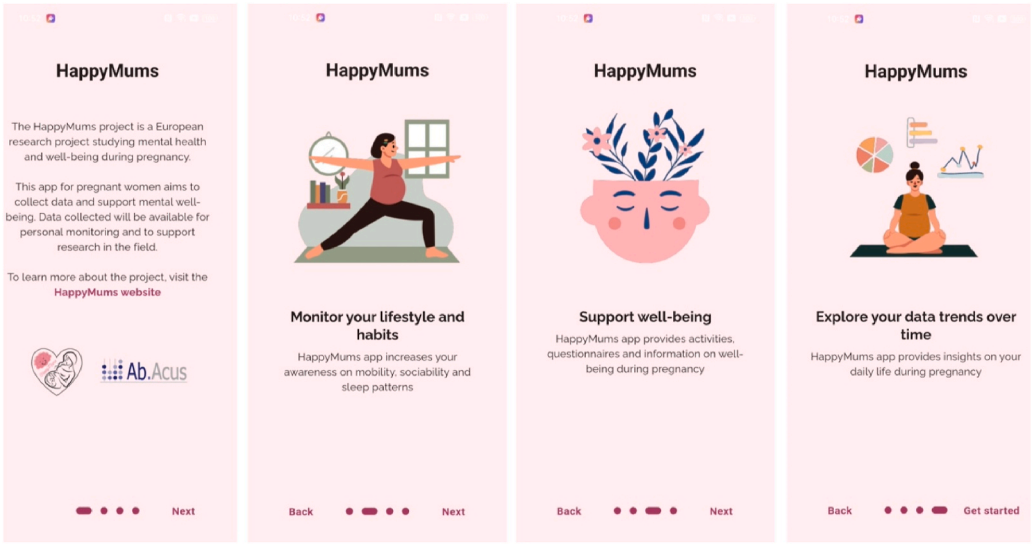

Fig. 6. Representation of HappyMums App
The HappyMums App for women will allow data collection, and specifically data will be generated by three different means: A) Manual data entry (completing questionnaires and periodically reporting medical and biological data); B) Active interaction with the system (voice analysis and facial expression modules and execution of game-like exercises); C) Passive monitoring (background collection of data coming from smartphone embedded sensors, such as physical and social activity).

main steps of the study include: 1) recruitment and screening of the women at high risk of or already suffering from antenatal depression; 2) online training of the users (clinicians, women, nurses, etc.) to use the platform; 3) patient data collection and management; 4) patient detailed clinical and psychological assessment. By running this large-scale screening, the project will assess different predictors (used as input in the model), their relative merits and potential limitations. After data extraction, machine learning approaches will be used to analyze data and build-up specific predictive models integrating different types of predictors. The utility and acceptability of the platform will then be tested using an in-silico approach across all the recruiting centres, to evaluate varying mental health systems and environments/cultures. Moreover, a subset of at least 210 women will undergo a more in-depth clinical interview. Rates of prediction of depression based on the App will be compared with the real-life results based on the direct assessment of women done by clinicians. Specific evaluation sessions will be carried out with experts in the field of perinatal mental health (psychiatrists, psychologists, mental health nurses, general researchers) to assess the usefulness and acceptability of the App and the dashboard. Based on the feedback/acceptance received, the HappyMums platform will undergo progressive improvements and adjustments to obtain a final version of the platform.

2.5. Concept 5 - effects of pharmacological and non-pharmacological interventions in pregnancy and underlying biology

Concept 5 will investigate the effect of pharmacological and non-pharmacological interventions in pregnancy and the underlying biology. HappyMums here will combine data from clinical cohorts with studies in animal models to test the efficacy of interventions in

pregnancy on women's mental health and to identify the mechanisms and biomarkers underlying this effect. We will identify novel pathways and targets that could be used to develop novel therapies or to repurpose already existing drugs. For the non-pharmacological intervention, the project will take advantage of a two-armed, parallel, superiority cluster-randomized clinical trial (cRCT), which aims to explore the therapeutic and/or preventive efficacy of an online, low-threshold, low-intensity, low-cost CBT-based self-help, stand-alone counselling intervention in pregnant women with clinically relevant depressive symptoms in early pregnancy. In HappyMums, this study will be used to identify biomarker responses and potential molecular mechanisms underlying the therapeutic and/or preventive effects of the eCBT. For the pharmacological intervention, the project will take advantage of an already ongoing study where pregnant women with depressive symptomatology receive a pharmacological intervention and are followed up to 1 year of age of the baby. Maternal blood samples, placental and foetal cord blood samples at delivery will be collected and used for subsequent biochemical and molecular analyses.

In addition to these clinical trials, the project will explore both non-pharmacological and pharmacological interventions in animal models. Specifically, a murine version of cognitive behavioural therapy (CBT), which is based on positively reinforced reversal learning, will be used for the non-pharmacological intervention. This murine-adapted CBT has already been shown to be able to prevent the effect of adverse exposures on behaviour (Havekes et al., 2006; Klarer et al., 2017). For the pharmacological intervention, dams will be treated with sertraline starting 4 weeks before mating and continuing throughout gestation and weaning of the offspring (Bérard et al., 2017; Mitchell et al., 2011). The underlying effect of the pharmacological intervention will be dissected by performing behavioural assessment, neuroimaging, and molecular analyses, in dams and their offspring.

2.6. Ethics and dissemination

The study has received ethical clearance from the European Commission. For the clinical study, each centre will obtain ethical approval to conduct the study. Similarly, for pre-clinical experiments, each centre will gain ethical approval. Furthermore, as part of the project, ethical guidelines to be followed when conducting psychiatric research and, in particular, when dealing with maternal/child health data and digital biomarkers will be produced. These will be the result of the review of the existing ethical guidelines and of all the actions and procedures adopted within the HappyMums study to comply with ethical regulations and further improve research practice.

The results of the study will be published in peer-reviewed academic journals and disseminated to and communicated with clinicians, researchers, patient organizations and media. A project website has been developed (https://www.happymums.eu/) and specific social media accounts have been created to disseminate information about perinatal mental illness and the HappyMums study, also to the general public. Finally, activities to promote the importance of perinatal mental health are routinely organised.

3. Discussion

In summary, HappyMums aims to investigate the important public health issue associated with the development of perinatal depressive symptoms. This translational line of research will help women and clinicians to identify personalized preventive or treatment strategies by using, for the first time in the perinatal mental health domain, the combined power of big and digital data within a dedicated platform, the use of both human data and animal models and the integration of biological, genetic and epigenetic biomarkers, with clinical, medical, lifestyle and environmental factors.

In particular, HappyMums will generate novel knowledge on clinical, biological, lifestyle, and environmental factors that contribute to depressive symptoms during the perinatal period and how these factors can influence the foetal programming of the exposed offspring, with potential negative effects on their development. HappyMums will also improve our understanding of the long-term impact of perinatal depression on offspring neurodevelopmental outcomes from birth to adolescence, and of the pre- and postnatal factors that could further influence the offspring's prenatally-primed vulnerability to develop negative outcomes, making some of them resilient.

Using this integrative approach to identify contributing factors and underlying mechanisms will mean that multi-disciplinary biomarkers or factors will be not only identified and measured separately but will also be integrated into unified statistical machine learning models. This will enable the identification of biomarkers for a reliable and accurate diagnosis and prognosis, allowing personalized risk prediction and interventions. Such biomarkers could then be made available to women, also outside the context of pregnancy, for assessing their mental health. This will lay the methodological foundation for new personalized medicine approaches. All this knowledge will also allow the identification of novel targets (e.g., biological mechanisms or pathways) that could be used for the development of novel classes of medications, the repurposing of already existing medications or the development of non-pharmacological interventions to prevent or treat depressive symptoms.

The development of a digital platform, specifically tailored to pregnant women, for early screening, and monitoring of symptom progression, will contribute to reforming our diagnostic system using a bottom-up approach based on the integration of heterogeneous data, instead of the current top-down approach based on our limited classification system. The App will allow continuous monitoring of symptomatology in women at high risk of depression, and this will contribute to maximizing early detection of symptoms and, therefore, prompt interventions, to protect both women and their children.

In future, we expect that the knowledge gained from the feasibility study on the APP could be used in the clinical setting for predicting disease progression, prompt diagnoses, personalized treatments and the promotion of protective lifestyle attitudes to maintain and improve mental health. Moreover, personalized feedbacks based on behavioural and outcome data could be provided directly to mothers, actively involving and empowering them to better monitor and manage their mental health and well-being and to interact with their healthcare providers. Overall, this will contribute to increasing awareness of perinatal depression and reducing the stigma associated with depression in pregnancy. This is a particularly important step towards a better care system where, as stated by the European Patients Forum, patients are 'experts by experience'. The active involvement of several patient associations (Tommy's and Marce Society) will help ensure that HappyMums meets the needs of these women and their families and empower women to seek help promptly.

The work of the HappyMums project will also contribute to an improvement of the current clinical guidelines in perinatal mental health. Indeed, by exploiting the extensive clinical expertise within the Consortium and engaging with stakeholders, especially those involved in the development of guidelines, results will contribute to updating clinical guidelines on maternal health during the perinatal period produced at national (e.g. the National Institute for Health and Care Excellence (NICE)) and International (WHO guidelines on maternal health) level, and to the design of new care paths, where digital tools can also be introduced in the clinical setting. Furthermore, the knowledge emerging from HappyMums will facilitate the adoption of a more comprehensive, psychobiological approach to maternal health and mother-child well-being.

Ultimately, the project is also expected to contribute to a wider impact at an economic level. Considering the number of births in Europe (Statista, 2023) and the economic cost associated with perinatal depression (Bauer et al., 2014, 2016), if HappyMums could improve the health condition of 1% of affected women, we estimate that the reduction of costs would amount to € 368 billion only in Europe.

In summary, the project is expected to produce clinically significant findings, with expected long-term benefits not only to women but also to their children, their families and the society at large.

4. Conclusion

In conclusion, the project is expected to increase our knowledge on perinatal depression by identifying the main risk and protective factors and underlying biological mechanisms associated with the onset and progression of depressive symptoms, testing the efficacy of interventions and understanding the potential impact of the illness on the offspring well-being and development.

This will contribute to promoting healthier lives of pregnant women and their families with a reduced disease burden and with positive effects also on the long-term development of their children and on society at different levels.

CRediT authorship contribution statement

A. Biaggi: Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **V. Zonca:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **C. Anacker:** Writing – review & editing, Methodology, Conceptualization. **V. Begni:** Writing – review & editing, Methodology, Conceptualization. **F. Benedetti:** Writing – review & editing, Methodology, Conceptualization. **A. Bramante:** Writing – review & editing, Methodology, Conceptualization. **A. Braniecka:** Writing – review & editing, Methodology, Conceptualization. **V. Brenna:** Writing – review & editing, Methodology, Conceptualization. **M. Bulgheroni:** Writing – review & editing, Methodology, Conceptualization. **C. Buss:** Writing – review & editing, Methodology, Conceptualization. **L. Cavaliere:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **C.A.M. Cecil:** Writing – review & editing, Methodology, Conceptualization. **A.C. Couch:** Writing – review & editing, Methodology, Conceptualization. **D. de Barra:** Writing – review & editing, Methodology, Conceptualization. **H. El Marroun:** Writing – review & editing, Methodology, Conceptualization. **S. Entringer:** Writing – review & editing, Methodology, Conceptualization. **R. Grassi-Oliveira:** Writing – review & editing, Methodology, Conceptualization. **M. Jackowska:** Writing – review & editing, Methodology, Conceptualization. **A. Korosi:** Writing – review & editing, Methodology, Conceptualization. **P.J.C. Kwant:** Writing – review & editing, Methodology, Conceptualization. **J. Lahti:** Writing – review & editing, Methodology, Conceptualization. **K. Lekadir:** Writing – review & editing, Methodology, Conceptualization. **I. Mansuy:** Writing – review & editing, Methodology, Conceptualization. **F. Manuella:** Writing – review & editing, Methodology, Conceptualization. M. Marizzoni: Writing – review & editing, Methodology, Conceptualization. **U. Meyer:** Writing – review & editing, Methodology, Conceptualization. **C. Monk:** Writing – review & editing, Methodology, Conceptualization. **S. Nakić Radoš:** Writing – review & editing, Methodology, Conceptualization. **C.M. Pariante:** Writing – review & editing, Methodology, Conceptualization. **B.J.A. Pollux:** Writing – review & editing, Methodology, Conceptualization. **K. Priestley:** Writing – review & editing, Methodology, Conceptualization. **K. Räikkönen:** Writing – review & editing, Methodology, Conceptualization. **J. Richetto:** Writing – review & editing, Methodology, Conceptualization. **M.A. Riva:** Writing – review & editing, Methodology, Conceptualization. **L.M. Rothmann:** Writing – review & editing, Methodology, Conceptualization. **V. Simonetti:** Writing – review & editing, Methodology, Conceptualization. **B. Vai:** Writing – review & editing, Methodology, Conceptualization. **A.C. Vernon:** Writing – review & editing, Methodology, Conceptualization. **M. Žutić:** Writing – review & editing, Methodology, Conceptualization. **A. Cattaneo:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors have nothing to declare.

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All authors reviewed and approved the final version of the manuscript.

Data availability

No data was used for the research described in the article.

References

Angelotta, C., Wisner, K.L., 2017. Treating depression during pregnancy: are We asking the Right Questions? Birth Defects Res 109 (12), 879–887. https://doi.org/10.1002/bdr2.1074.

Bauer, A., Knapp, M., Parsonage, M., 2016. Lifetime costs of perinatal anxiety and depression. J. Affect. Disord. 192, 83–90. https://doi.org/10.1016/j.jad.2015.12.005.

Bauer, A., Parsonage, M., Knapp, M., Iemmi, V., Adelaja, B., 2014. The Costs of Perinatal Mental Health Problems.

Bérard, A., Zhao, J.P., Sheehy, O., 2017. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort. BMJ Open 7 (1), e013372. https://doi.org/10.1136/bmjopen-2016-013372.

Biaggi, A., Conroy, S., Pawlby, S., Pariante, C.M., 2016. Identifying the women at risk of antenatal anxiety and depression: a systematic review. J. Affect. Disord. 191, 62–77. https://doi.org/10.1016/j.jad.2015.11.014.

Born, L., Zinga, D., Phillips, S.D., 2006. Update on the treatment of depression during pregnancy. Clin. Pract. 3 (1), 153.

Byatt, N., Biebel, K., Friedman, L., Debordes-Jackson, G., Ziedonis, D., Pbert, L., 2013. Patient's views on depression care in obstetric settings: how do they compare to the views of perinatal health care professionals? Gen. Hosp. Psychiatry 35 (6), 598–604. https://doi.org/10.1016/j.genhosppsych.2013.07.011.

Cao-Lei, L., de Rooij, S.R., King, S., Matthews, S.G., Metz, G.A.S., Roseboom, T.J., Szyf, M., 2020. Prenatal stress and epigenetics. Neurosci. Biobehav. Rev. 117, 198–210. https://doi.org/10.1016/j.neubiorev.2017.05.016.

Furness, A.I., Pollux, B.J.A., Meredith, R.W., Springer, M.S., Reznick, D.N., 2019. How conflict shapes evolution in poeciliid fishes. Nat. Commun. 10 (1), 3335. https://doi.org/10.1038/s41467-019-11307-5.

Garcia-Toro, M., Aguirre, I., 2007. Biopsychosocial model in Depression revisited. Med. Hypotheses 68 (3), 683–691. https://doi.org/10.1016/j.mehy.2006.02.049.

Havekes, R., Nijholt, I.M., Luiten, P.G., Van der Zee, E.A., 2006. Differential involvement of hippocampal calcineurin during learning and reversal learning in a Y-maze task. Learn. Mem. 13 (6), 753–759. https://doi.org/10.1101/lm.323606.

Hay, D.F., Pawlby, S., Waters, C.S., Sharp, D., 2008. Antepartum and postpartum exposure to maternal depression: different effects on different adolescent outcomes. J Child Psychol Psychiatry 49 (10), 1079–1088. https://doi.org/10.1111/j.1469-7610.2008.01959.x.

Hussain-Shamsy, N., Shah, A., Vigod, S.N., Zaheer, J., Seto, E., 2020. Mobile health for perinatal depression and anxiety: Scoping review. J. Med. Internet Res. 22 (4), e17011. https://doi.org/10.2196/17011.

Iyengar, U., Jaiprakash, B., Haitsuka, H., Kim, S., 2021. One Year into the pandemic: a systematic review of perinatal mental health outcomes during COVID-19. Front Psychiatry 12, 674194. https://doi.org/10.3389/fpsyt.2021.674194.

Klarer, M., Weber-Stadlbauer, U., Arnold, M., Langhans, W., Meyer, U., 2017. Cognitive effects of subdiaphragmatic vagal deafferentation in rats. Neurobiol. Learn. Mem. 142 (Pt B), 190–199. https://doi.org/10.1016/j.nlm.2017.05.006.

Koss, K.J., Gunnar, M.R., 2018. Annual Research Review: early adversity, the hypothalamic-pituitary-adrenocortical axis, and child psychopathology. J Child Psychol Psychiatry 59 (4), 327–346. https://doi.org/10.1111/jcpp.12784.

Kreitz, S., Zambon, A., Ronovsky, M., Budinsky, L., Helbich, T.H., Sideromenos, S., Pollak, D.D., 2020. Maternal immune activation during pregnancy impacts on brain structure and function in the adult offspring. Brain Behav. Immun. 83, 56–67. https://doi.org/10.1016/j.bbi.2019.09.011.

Lahti, M., Savolainen, K., Tuovinen, S., Pesonen, A.-K., Lahti, J., Heinonen, K., Räikkönen, K., 2017. Maternal depressive symptoms during and after pregnancy and psychiatric Problems in children. Journal of the American Academy of Child & Adolescent Psychiatry 56 (1), 30–39.e37. https://doi.org/10.1016/j.jaac.2016.10.007.

Lin, P.Y., Chiu, T.H., Ho, M., Pei-Chen Chang, J., Hui-Chih Chang, C., Su, K.P., 2019. Major depressive episodes during pregnancy and after childbirth: a prospective longitudinal study in Taiwan. J. Formos. Med. Assoc. 118 (11), 1551–1559. https://doi.org/10.1016/j.jfma.2019.03.003.

Milgrom, J., Gemmill, A.W., Bilszta, J.L., Hayes, B., Barnett, B., Brooks, J., Buist, A., 2008. Antenatal risk factors for postnatal depression: a large prospective study. J. Affect. Disord. 108 (1–2), 147–157. https://doi.org/10.1016/j.jad.2007.10.014.

Mitchell, A.A., Gilboa, S.M., Werler, M.M., Kelley, K.E., Louik, C., Hernández-Díaz, S., 2011. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am. J. Obstet. Gynecol. 205 (1), 51.e51–51.e58. https://doi.org/10.1016/j.ajog.2011.02.029.

Mueller, F.S., Scarborough, J., Schalbetter, S.M., Richetto, J., Kim, E., Couch, A., Meyer, U., 2021. Behavioral, neuroanatomical, and molecular correlates of resilience and susceptibility to maternal immune activation. Mol. Psychiatr. 26 (2), 396–410. https://doi.org/10.1038/s41380-020-00952-8.

Munodawafa, M., Mall, S., Lund, C., Schneider, M., 2018. Process evaluations of task sharing interventions for perinatal depression in low and middle income countries (LMIC): a systematic review and qualitative meta-synthesis. BMC Health Serv. Res. 18 (1), 205. https://doi.org/10.1186/s12913-018-3030-0.

Norhayati, M.N., Hazlina, N.H., Asrenee, A.R., Emilin, W.M., 2015. Magnitude and risk factors for postpartum symptoms: a literature review. J. Affect. Disord. 175, 34–52. https://doi.org/10.1016/j.jad.2014.12.041.

Pollux, B.J., Meredith, R.W., Springer, M.S., Garland, T., Reznick, D.N., 2014. The evolution of the placenta drives a shift in sexual selection in livebearing fish. Nature 513 (7517), 233–236. https://doi.org/10.1038/nature13451.

Pollux, B.J., Pires, M.N., Banet, A.I., Reznick, D.N., 2009. Evolution of placentas in the fish family Poeciliidae: an Empirical study of Macroevolution. Annual Review of Ecology, Evolution, and Systematics 40, 271–289. https://doi.org/10.1146/annurev.ecolsys.110308.120209, 40, 2009.

Rogers, A., Obst, S., Teague, S.J., Rossen, L., Spry, E.A., Macdonald, J.A., Hutchinson, D., 2020. Association between maternal perinatal depression and anxiety and child and adolescent development: a meta-analysis. JAMA Pediatr. 174 (11), 1082–1092. https://doi.org/10.1001/jamapediatrics.2020.2910.

Safian, D., Ahmed, M., van Kruistum, H., Furness, A.I., Reznick, D.N., Wiegertjes, G.F., Pollux, B.J.A., 2023. Repeated independent origins of the placenta reveal convergent and divergent organ evolution within a single fish family (Poeciliidae). Sci. Adv. 9 (34), eadf3915. https://doi.org/10.1126/sciadv.adf3915.

Scarborough, J., Mueller, F.S., Weber-Stadlbauer, U., Mattei, D., Opitz, L., Cattaneo, A., Richetto, J., 2021. A novel murine model to study the impact of maternal depression and antidepressant treatment on biobehavioral functions in the offspring. Mol Psychiatry 26 (11), 6756–6772. https://doi.org/10.1038/s41380-021-01145-7.

Serati, M., Redaelli, M., Buoli, M., Altamura, A.C., 2016. Perinatal major depression biomarkers: a systematic review. J. Affect. Disord. 193, 391–404. https://doi.org/10.1016/j.jad.2016.01.027.

Statista, 2023. Number of live births in the European Union (EU27) from 2009 to 2022. Retrieved from. https://www.statista.com/statistics/253401/number-of-live-births-in-the-eu/.

Stein, A., Pearson, R.M., Goodman, S.H., Rapa, E., Rahman, A., McCallum, M., Pariante, C.M., 2014. Effects of perinatal mental disorders on the fetus and child. Lancet 384 (9956), 1800–1819. https://doi.org/10.1016/s0140-6736(14)61277-0.

Suarez, A., Lahti, J., Czamara, D., Lahti-Pulkkinen, M., Knight, A.K., Girchenko, P., Räikkönen, K., 2018. The epigenetic Clock at birth: associations with maternal antenatal depression and child psychiatric Problems. J. Am. Acad. Child Adolesc. Psychiatry 57 (5), 321–328.e322. https://doi.org/10.1016/j.jaac.2018.02.011.

Tuovinen, S., Lahti-Pulkkinen, M., Girchenko, P., Heinonen, K., Lahti, J., Reynolds, R.M., Raikkonen, K., 2021. Maternal antenatal stress and mental and behavioral disorders in their children. J. Affect. Disord. 278, 57–65. https://doi.org/10.1016/j.jad.2020.09.063.

van Kruistum, H., Nijland, R., Reznick, D.N., Groenen, M.A.M., Megens, H.J., Pollux, B.J.A., 2021. Parallel genomic changes drive repeated evolution of placentas in live-bearing fish. Mol. Biol. Evol. 38 (6), 2627–2638. https://doi.org/10.1093/molbev/msab057.

Weinstock, M., 2017. Prenatal stressors in rodents: effects on behavior. Neurobiol Stress 6, 3–13. https://doi.org/10.1016/j.ynstr.2016.08.004.

Weiss, I.C., Franklin, T.B., Vizi, S., Mansuy, I.M., 2011. Inheritable effect of unpredictable maternal separation on behavioral responses in mice. Front. Behav. Neurosci. 5, 3. https://doi.org/10.3389/fnbeh.2011.00003.

Zou, R., Tiemeier, H., van der Ende, J., Verhulst, F.C., Muetzel, R.L., White, T., El Marroun, H., 2019. Exposure to maternal depressive symptoms in Fetal life or childhood and offspring brain development: a population-based Imaging study. Am J Psychiatry 176 (9), 702–710. https://doi.org/10.1176/appi.ajp.2019.18080970.