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ABSTRACT

Maternal prenatal depression is common during pregnancy, yet its effects on placental biology remain poorly understood. We investigated the association between cumulative maternal depressive symptoms during pregnancy and the placental proteome.

We profiled 96 placental samples from the FinnBrain Birth Cohort. Maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) at 14, 24, and 34 weeks' gestation. Mean EPDS scores stratified participants into low (n = 49), moderate (n = 20), and high (n = 27) depressive symptom groups.

Depressive symptom severity showed modest associations with the placental proteome, with nine placental proteins shared between the moderate- and high-symptom groups. Although only one protein, LIMCH1, survived correction for multiple testing, pathway-level alterations involving steroid biosynthesis and extracellular matrix integrity were implicated in both exposure groups. Importantly, the interaction between maternal depressive symptoms and foetal sex was stronger than the main effect of depressive symptoms alone. This interaction encompassed 238 nominally differentially expressed proteins, with alterations in protein synthesis, ubiquitination, energy metabolism, cytoskeletal integrity, and immune signalling pathways.

These findings provide preliminary evidence that maternal depressive symptoms are associated with modest alterations in the placental proteome, while revealing a sex-dependent molecular response. Placentas from male infants showed more protein changes associated with moderate-depressive symptoms, than those from female infants. These findings suggest that foetal sex may modify placental responses to maternal depressive symptoms and provide a potential biological mechanism through which prenatal stress may contribute to sex-specific developmental vulnerability. Replication in larger, independent cohorts is warranted.

INTRODUCTION

Pregnancy is a major transitionary period for women, and a time of amplified vulnerability to psychological stress (1). Maternal prenatal depression is among the most prevalent mental health condition experienced during this time (2). Prenatal depression has been associated with various obstetric complications such as preeclampsia, intrauterine growth restriction, gestational diabetes, low birth weight, and preterm birth, resulting in poorer neonatal and child health outcomes (3–5). These effects reflect early biological maternal stress, which has been shown to shape offspring health trajectories and developmental outcomes. An estimated 10–20% of pregnant women globally (6–9), and up to 25% in low and middle-income countries experience clinically significant depressive symptoms during pregnancy (10). Symptoms of depression during the prenatal period often go undiagnosed and undertreated (11–13), or are attributed to normal hormonal changes and are consequently overlooked. Thus, prenatal depression is frequently underreported, resulting in large discrepancies in prevalence rates across studies and within regions (9).

Mounting evidence underscores the impact of prenatal depression on maternal physiology, pregnancy, and developmental trajectories of the infant (8,14). Intrauterine exposures, such as psychological stress can epigenetically and metabolically program foetal health and long-term health outcomes (15–17). Further evidence of biological disruption has been suggested, with research illustrating differential DNA methylation in umbilical cord blood (18–20) and placenta tissue (7), where prenatal maternal depressive symptoms were implicated. Findings from these studies identified specific epigenetic alterations in genes related to neurodevelopment, immune function, and metabolic regulation. Further, a systematic review reported that maternal prenatal depression is associated with heightened inflammation and stress responses, negatively affecting nutrient transport and placental hormone regulation (8).

Animal studies have investigated sex differences in the placental molecular profile and demonstrate epigenetic changes in a sex-dependant manner (21–23). Similarly, human studies suggest that sex-specific patterns of placental gene regulation and histone modifications, including those linked to nutrient signalling, support the placenta's role in sexual dimorphisms, and explain sex-specific vulnerabilities in utero (24). Human studies show variable findings, but evidence suggests that placentas from male infants prioritise growth and proliferation, while placentas from female infants exhibit more modest growth and increased resilience to oxidative stress (25). However, this pattern is not consistent across all research, representing a limitation in the current literature.

Placental research has mainly focused on genetics and epigenetics, while proteomics remains underexplored in relation to maternal depression. Proteins are direct, rapidly

responsive effectors of environmental stress, and pathways such as immunomodulation, angiogenesis, and energy metabolism are essential for placental function and foetal development (26,27). However, the effects of how maternal depressive symptoms affect the placental proteome is poorly understood. Definitions of maternal depression vary across studies, and a formal clinical diagnosis is not always clearly specified. Here, we define prenatal depressive symptoms by the Edinburgh Postnatal Depression Scale (EPDS) scores; this measure is not a formal clinical diagnosis of major depressive disorder (MDD). Using maternal clinical data and placenta samples from the FinnBrain Birth Cohort (14), we characterised placental proteomes from mothers with low, moderate, and high symptom levels. We therefore examined whether prenatal depressive symptoms were associated with changes in placental protein expression.

MATERIALS AND METHODS

For extended materials and methods please refer to supplementary information.

Study Participants

This study is nested within the FinnBrain Birth Cohort, a population-based prospective cohort study, designed to investigate the effects of early life stress on offspring neurodevelopment and long-term health outcomes, with the potential of biomarker discovery (14). Establishment of the birth cohort was based on the understanding that prenatal stressful events, including maternal mental health, can have profound effects on the developing infant, which persist into adulthood. Between December 2011 and April 2015, a total of 3,808 pregnant women and 2,623 partners were recruited by research nurses during routine first-trimester ultrasound visits at approximately 12 weeks' gestation. Recruitment occurred across three predefined maternal welfare clinics in the Southwest hospital district of Finland, where all women are subsequently referred to and affiliated with Turku University Hospital, thereby aiding participant follow-up and consistency in sample collection. Recruitment was contingent upon a normal first-trimester screening result, a good understanding of Swedish or Finnish and living within the catchment area of the hospital district. Infant health and developmental outcomes were followed through parental consent, resulting in the enrolment of 3,837 children, inclusive of 29 twin pairs.

At delivery, tissue samples from both the maternal and foetal surfaces of the placenta were obtained from a sub population of 252 women. Of the 252 maternal-side placental samples, 96 were selected for proteomic analysis based on completeness of questionnaire data and sample integrity. This proteomic subset overlaps with those used in a prior epigenetic study by Lund et al., (2021), which demonstrated that placental DNA methylation marks are associated with maternal depressive symptoms during early pregnancy (7). Building upon this work, the current study applies proteomic profiling to the same sample-set, to explore downstream molecular consequences of prenatal depressive symptoms at the level of protein expression. In accordance with the Declaration of Helsinki, the study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland.

Psychological Measures and Study Design

Maternal depressive symptoms were assessed at three timepoints during pregnancy, 14-, 24-, and 34-weeks' gestation. Self-reported data was collected using EPDS scores, which has been validated for prenatal and postnatal populations. The EPDS is a 10-item

questionnaire designed to screen for depressive symptoms over the previous seven days. Each item is scored on a four-point Likert scale (0–3), yielding a total score ranging from 0 to 30 (28). It is widely used in both clinical and research settings to identify women at risk for perinatal depression (29).

To capture the cumulative burden of depressive symptoms during pregnancy, we computed the mean EPDS score, using all three gestational time points (14, 24, and 34 weeks') (30). Participants were subsequently categorized into one of three groups: Low EPDS: 0–4; Moderate EPDS: 5–9; High EPDS: ≥10 (Table 1). These categories were selected to reflect subclinical to clinically meaningful levels of depressive symptoms. In clinical practice, EPDS scores are typically interpreted as follows: scores of 7-13 suggest moderate depression, and scores ≥13 indicate increased risk for MDD. While cut-offs may vary by setting, scores below 10 are generally considered to reflect transient mood changes that do not significantly impair day to day functioning, whereas scores of 10–13 may warrant clinical follow-up, and scores ≥13 often prompt active intervention (28,29).

Participant demographic and clinical variables, including maternal age, pre-pregnancy BMI, gestational diabetes, smoking during pregnancy, infant sex, infant gestational age at birth, mode of delivery, and the time interval from placental delivery to sample freezing are summarized by participant group (low, moderate, and high) in Table 1. Data presented is mostly register-based data, as well as self-reported by participants. To assess differences across participant groups, we used a Univariate General Linear Model (GLM) with Tukey's HSD post-hoc pairwise comparisons for parametric continuous variables, and the Kruskal–Wallis test with Mann–Whitney U tests for post-hoc pairwise comparisons for non-parametric continuous variables. Pearson's chi-squared test was used for categorical variables (e.g., infant sex, delivery mode). Statistical significance was set at $p < 0.05$. All analyses were performed in SPSS v29.0.2.0.

Placental Tissue Collection

Placenta samples harvested from the maternal (basal) surface were used in this study. Samples were collected within one hour of delivery, snap frozen in liquid nitrogen and stored at −70°C in a monitored biobank facility. Samples were transferred to University College Cork (UCC), in September 2022 for proteomic analysis.

Placental Tissue Preparation and Protein Extraction

Approximately 40mg of each placenta tissue sample was weighed and solubilised in 400µL of 8M urea-based lysis buffer. Homogenates were centrifuged at 15,000 × g for 10 minutes at 4°C, and the supernatant was collected. Total protein concentration was quantified using the Pierce® BCA Protein Assay Kit (Thermo Scientific, Ireland) according

to manufacturer's instructions. Based on measured protein concentrations, all samples were diluted to approximately 1µg/µL in 1M urea buffer for digestion reactions.

Protein Digestion and Clean-up

Each sample underwent standardised reduction, alkylation, and enzymatic digestion with dithiothreitol (DTT; Sigma-Aldrich, Ireland), iodoacetamide (IAA; Sigma-Aldrich, Ireland) and sequencing-grade trypsin (Promega, Ireland) at a 1:50 enzyme-to-protein ratio. Digestion was quenched with 10% formic acid (FA; Sigma-Aldrich, Ireland) and evaporated to dryness. For sample cleanup and desalting, C18 ZipTips® (Millipore, Merck, Ireland), were utilised.

Mass Spectrometry Analysis

Quantitative proteomic profiling of placental tissue samples was conducted using LC-MS/MS on a timsTOF Pro mass spectrometer (Bruker Daltonics, Bremen, Germany) operated in Data-Independent Acquisition – Parallel Accumulation–Serial Fragmentation (DIA-PASEF) mode, as described previously (31,32).

Data pre-processing

Raw mass spectrometry data were analysed using FragPipe version 18.0. The built-in DIA-SpecLib_Quant workflow was employed for Data-Independent Acquisition (DIA) datasets, encompassing peptide identification, spectral library generation, and protein quantification. Perseus (version 2.1.4.0) was employed for data pre-processing (33). Samples were grouped based on maternal EPDS scores (Low: 0–4, Moderate: 5–9, High: ≥10) and infant sex (Male/Female). Proteins present in >70% of samples per group were retained for quantification. Data were log2-transformed and normalised by subtracting the median intensity for each sample (column-wise normalisation).

Statistical analysis

All subsequent analyses were performed in R (version 4.3.2) using RStudio (version 2025.05.0.496). *Partial Least Squares Discriminant Analysis (PLS-DA)* was performed, whereby missing values were imputed using Bayesian Principal Component Analysis, in the *pcaMethods* package. Supervised classification was performed using PLS-DA in the *mixOmics* package. The imputed protein expression matrix was modelled against maternal participant groups (Low, Moderate, High) as a categorical outcome variable, and models were constructed using two components. Sample scores were visualised

with 95% confidence ellipses. Variable Importance in Projection (VIP) scores were extracted for each protein and component. Average VIP scores across the two components were calculated, and the top-ranked proteins (n = 20) were exported for downstream interpretation.

General Linear Models. Differential protein expression was assessed using the non-imputed dataset. First, univariate GLMs were fitted, with maternal participant group (-Low, -Moderate, -High Depression) as the sole independent variable. Next, two-way GLMs were fitted, including maternal EPDS and foetal sex (Boy, Girl), and their interaction. Resulting *p*-values were adjusted for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) procedure (34). Post hoc pairwise comparisons were performed using estimated marginal means with Tukey adjustment for multiple comparisons (*emmeans* package). Group-wise means were used to compute log2 fold changes for each comparison.

Volcano plots. To visualise differential protein abundance between Moderate vs Low and High vs Low depressive symptom groups, we employed volcano plots. Proteins were filtered to those showing nominal evidence of an overall effect of maternal depression in the univariate GLM ($p < 0.05$). For each comparison, log2 fold change was plotted on the x-axis and −log10(*p*-value) from Tukey post hoc tests on the y-axis.

Clustering of sex-specific responses. Proteins showing a nominal significant interaction between maternal symptoms and foetal sex ($p < 0.05$, two-way GLM) were selected for heatmap visualisation. For each protein, log2 fold-change between-group estimates were extracted, the resulting contrast matrix was scaled (z-scored) across proteins and subjected to unsupervised k-means clustering (k = 6, 50 random starts). Heatmaps were generated using the *pheatmap* package. A diverging blue–white–red colour scale represented relative decreases and increases in protein abundance in the Moderate and High EPDS groups relative to Low score controls. All figures were generated using *ggplot2*.

Functional pathway analysis

To explore the broad molecular processes altered in the placenta in response to maternal depressive symptoms and associated sex-specific effects, all nominally differentially expressed proteins ($p < 0.05$) were analysed using STRING (version 12.0; https://string-db.org/) (35).

RESULTS

Study Participants

Clinical demographics and participant groups are described in Table 1. No significant differences in potential confounders were observed between depressive symptom groups.

Proteomic Profiling of the Placenta Reveals Modest Molecular Signatures of Maternal Depressive Symptoms

After filtering for proteins present in at least 70% of samples per group, 2,840 proteins were retained for quantification between groups. Supervised classification with Partial Least Squares Discriminant Analysis (PLS-DA) revealed modest separation between depressive symptom groups, with the strongest shift observed between the High vs Low symptom groups (**Figure 1A**). The Variable Importance in Projection (VIP) plot shows the top 20 proteins driving this separation (**Figure 1B**). Differential expression analysis was performed using general linear models with maternal depression as the independent factor. We identified 184 proteins as nominally associated with maternal depressive symptoms ($p < 0.05$; Supplementary Tables S1-S2), and one protein LIMCH1, remained significant after FDR correction ($q < 0.05$). Subsequent post-hoc pairwise comparisons between Moderate vs Low, and High vs Low depression symptom groups, revealed differential expression of 71 proteins (moderate vs. low), and 79 proteins (high vs low) at nominal significance ($p < 0.05$; **Figure 1C-D**; Supplementary Table S2). No proteins remained significant following FDR correction for multiple testing. STRING pathway analysis of the nominally differentially expressed proteins (71 and 79 proteins, respectively) implicated subtle alterations in steroid hormone metabolism, extracellular matrix signalling, lipid metabolism, and nuclear pore complex pathways in response to maternal depressive symptoms (**Figure 1E, 1F**).

Importantly, we identified nine proteins -ADH1C, BCAS2, GOLGA2, HSD3B2, LIMCH1, NUP188, NUP37, TRIM29, TXNDC5 as altered in both moderate- and high-depressive symptom groups compared to low-depression controls ($p < 0.05$; **Figure 2**). All proteins shared between the moderate- and high-depressive symptom groups were among the top 20 features from the PLS-DA model (**Figure 1B**).

INSERT FIGURE 1 HERE

INSERT FIGURE 2 HERE

Foetal Sex and Depressive Symptom Severity Influence Distinct Placental Protein Response Patterns.

We further examined sex-shared and sex-divergent protein responses to moderate- and high- maternal depressive symptoms. We observed that most altered proteins showed a similar direction of change between placentas of male and female infants (**Figure 3A-B**). In the moderate depressive symptom group only, the effect sizes of altered proteins were consistently larger in male placentas across symptom groups, in comparison to placentas from females, suggesting increased vulnerability in males to prenatal stress. Furthermore, two-way GLM analysis unmasked over 40 proteins with sex-dependent responses to depressive symptoms (**Figure 3C-D**), that were not detected in our initial analysis, as opposing protein changes between male and female placentas masked these sex-specific effects. We subsequently examined all proteins showing evidence of a depression × foetal sex interaction, including those not detected in post hoc tests (Supplementary Tables S3-S4). In total, 238 proteins showed a nominally significant interaction effect (non-adjusted $p < 0.05$, two-way GLM), which was more prominent than the main effect of maternal depressive symptoms.

INSERT FIGURE 3 HERE

To visualise patterns of sex-specific protein responses, we performed heatmap clustering analysis, which identified six protein clusters (**Figure 4A**). Clusters 1, 6, 3, and 4 are illustrated in **Figure 4**(**B-E**). Clusters 2 and 5 are shown in **Supplementary Figure 2**(**B-C**).

Across clusters, we observed distinct sex-specific and severity-dependent patterns in the placental protein response to maternal depression. In clusters 1, 3, 4, and 6, relative protein abundances showed opposing trends between male and female placentas. Functionally, the clusters converged on distinct biological processes. Clusters 1, 2, 5, and 6 were commonly associated with protein synthesis, protein folding, and proteasomal activity, with clusters 1 and 5 further implicating ubiquitination. Cluster 1 was strongly enriched for cytoskeletal organisation (ANXA1, ANXA3, ANXA6). In contrast, cluster 5 was enriched for energy metabolism (AGL, UGP2, PFKM, GPD1L, ACOX1, ACSS1, GLUD1, PPA2). Clusters 3 and 4 both converged on extracellular matrix structural constituents, implicating cytoskeletal processes such as cell adhesion, invasion, proliferation, and vascular remodelling. However, they diverged in additional pathways: Cluster 3 was associated with lipid metabolism (MGLL, HPCAL1), while cluster 4 mapped to immune-related complement and coagulation cascades (C4BPA, C7, C8A, CD9, CFI, HABP2, CLU, FGG, PLG, SERPINF2, CP, FECH), further centring on DNA damage repair

pathways (APEX1, RPA1). In summary, clustering revealed nominal sex-specific changes in response to maternal depressive symptoms including pathways involved in protein synthesis, ubiquitination, energy metabolism, cellular transport, cytoskeletal integrity, and immune signalling. Broadly, these molecular alterations point to subtle dysregulation of upstream regulatory pathways, including mTOR, EIF, MAP kinase, and PI3K-AKT signalling.

INSERT FIGURE 4 HERE

DISCUSSION

This is the first human investigation of the placental proteome in relation to prenatal maternal depression. Prenatal depressive symptoms were associated with modest, predominantly nominal changes in the placental proteome. Although nine proteins showed consistent dysregulation in both moderate and high symptom groups, only LIMCH1 survived correction for multiple testing, indicating that the overall impact of maternal depressive symptoms on placental protein expression is not profound. However, a more nuanced picture emerged when considering foetal sex. We observed an interaction between maternal depressive symptoms and foetal sex that was stronger than the main effect of depression alone, encompassing 238 nominally differentially expressed proteins, and alterations converging in pathways related to protein synthesis and ubiquitination, energy metabolism, cytoskeletal integrity, and immune signalling. In the moderate-depressive symptom group, placentas from male infants exhibited more depression-associated changes than those from female infants. Overall, these findings indicate that while the global placental proteome is largely resilient to maternal depressive symptoms, a subtle but biologically plausible sex-dependent response exists.

Nine proteins were dysregulated in both moderate- and high- symptom groups (ADH1C, BCAS2, GOLGA2, HSD3B2, LIMCH1, NUP188, NUP37, TRIM29, TXNDC5; Figure 2); while others were unique to severity level (Figure 1C-D), warranting replication in larger cohorts with clinically diagnosed depression. We also observed dysregulation of proteins with functions in steroid hormone biosynthesis in moderate- (n = 4; HSD3B1, HSD3B2, HSD17B11, PRKACA) and high-symptom groups (n= 7; POR, HSD3B2, CYP11A1, SULT2B1, G6PD, CBR1, AKR1A1) in comparison to the low symptom controls. Notably, CYP11A1 initiates steroid synthesis with the conversion of cholesterol into pregnenolone (36), while HSD3B1, and HSD3B2, catalyse key reactions that produce progesterone, androstenedione, and the inactive cortisone. HSD17B11 further regulates steroid hormone homeostasis (36,37). Steroid hormone biosynthesis is closely linked to lipid metabolism and energy production, which are vital for foetal development (38,39). Altered steroidogenesis has been associated with obstetric complications and autism (32,40–43). Altered ECM signalling pathways were also observed in both moderate and high symptom groups. ECM proteins are essential regulators of placental architecture, vascular function, nutrient transfer, immune protection, and cellular signalling. Disrupted ECM integrity compromises placental efficiency, affecting foetal growth and neurodevelopment (44,45). Altered ECM signalling is implicated in neurodevelopmental conditions (45) and detectable in cord blood from children with autism (46). Collectively, modest alterations in steroid- and ECM- signalling observed across symptom groups are noteworthy in the context of prenatal environmental stress and altered

neurodevelopmental trajectories. These findings underscore the importance of understanding susceptibility within these placental networks in response to prenatal depression.

Our findings further demonstrate that the effect of maternal depressive symptoms on the placenta is shaped by foetal sex, rather than acting uniformly across pregnancies. These nuanced sex-specific molecular alterations may be indicative of dysregulation in upstream regulatory pathways such as mTOR, EIF, MAP kinase, and PI3K-AKT signalling, pointing to functional consequences at the maternal-foetal interface. Sex differences in response to prenatal environmental stimuli are increasingly recognised as critical determinants of developmental outcomes (23,25,47). While sex dimorphisms have been well characterised in animal studies (23,48), human studies examining sex-specific effects of prenatal stress are limited (7,23,49). The findings presented here align with the female protective effect, and the heightened sensitivity of the males may represent a key mechanism driving sex-biased vulnerabilities in neurodevelopmental conditions (1,25,50,51). However, replication in larger independent cohorts is warranted.

A focus on prenatal maternal depression research is critically important, given the extent of intrauterine alterations and adverse maternal and infant outcomes attributed to poor maternal mental health (3,9,20,52–54). Although healthcare policies and procedures exist to identify maternal depression (9,55–58), most prioritise postpartum depression, with insufficient attention to prenatal depression and interventions (59). Effective treatment of maternal depression with appropriate and timely interventions has demonstrated potential for improving health outcomes (30). Brief interpersonal therapy during pregnancy is emerging as an adjuvant measure to reduce prenatal depressive symptoms, especially for women experiencing mild-moderate depression (59). Selective Serotonin Reuptake Inhibitors (SSRIs) are the most common antidepressants prescribed for the treatment of maternal depression during pregnancy. Their potential effects on infant neurodevelopment have therefore been thoroughly researched (2,60), with inconsistent results/however results are inconsistent. Reassuringly, a recent meta-analysis of 27 studies found little evidence to suggest that SSRIs during pregnancy increase the likelihood of Autism or ADHD in exposed offspring (61). When influencing factors such as family history and maternal mental health were accounted for, evidence for a direct cause-and-effect relationship between SSRI's and neurodivergent outcomes were low. The authors conclude that pregnant women with moderate to severe depression should continue antidepressant treatment (60,61). SSRI treatment in women with prenatal depression was also found to reduce placental alterations in proteins linked to placental senescence, platelet activation, and amyloid fiber formation compared with non-treated mothers (2), offering further reassurances in the clinical management of maternal prenatal depression.

This study has several strengths and limitations. This is the first investigation using proteomic profiling of human placental tissue to examine the interaction between prenatal maternal depressive symptoms and foetal sex. This approach revealed the placental response is sex-dependent, a finding that would have been obscured in sex-agnostic analyses. Several limitations should be acknowledged. First, the overall severity of depressive symptoms in the cohort was low, with just three mothers reporting use of SSRIs during pregnancy, which may have constrained our ability to detect more robust protein-level changes. Although participant groups were well matched, the overall sample size (n=96) is relatively modest and future work in larger pregnancy cohorts to replicate findings is warranted. Second, as we computed a mean EPDS score, averaged across all three trimesters, we were unable to examine potential timing effects of prenatal depression. We intentionally focused on capturing the cumulative burden of depressive symptoms, reasoning that this approach would maximise our ability to detect robust placental proteome changes in response to persistent prenatal depressive symptoms. Crucially, the foetal brain is unique in its prolonged development across all trimesters, rendering it particularly vulnerable to cumulative stressors. Future work in larger, well-powered cohorts is needed to investigate placental vulnerability to stress exposure across different time sensitive windows. Third, our focus on the maternal surface of the placenta provides a limited snapshot of complex placental biology. We focused on the maternal subregion to reduce placental heterogeneity, an approach which was informed by our previous work demonstrating proteomic differences between maternal-, mid- and foetal- placental subregions (27). In Manna et al., (2023) we established, the maternal subregion exhibits distinct functions related to energy metabolism, cellular senescence, and immune function (27). Building on this knowledge, our findings reveal that maternal depressive symptoms dysregulate these pathways in a sex-dependent manner, suggesting that maternal depression subtly disrupts existing physiological networks rather than engaging entirely novel molecular signatures. The observed changes likely extend to all placental regions, and future work examining the foetal surface of the placenta could reveal additional or corroborating alterations.

In conclusion, this study provides evidence that prenatal maternal depressive symptoms are associated with nominal alterations in the human placental proteome, implicating steroid hormone and ECM signalling pathways across symptom groups. Although these protein changes did not survive adjustment for multiple comparisons, they suggest that maternal depressive symptoms exert limited rather than profound effects on placental biology. More notably, we observed a sex-dependent response, which may represent a biological mechanism linking prenatal stress exposure to the established sex-biases observed in neurodevelopmental conditions. These findings suggest that the males are uniquely sensitive to maternal depressive symptoms, warranting replication in larger, independent cohorts before drawing firm clinical conclusions.

Competing interests

The authors declare no competing interests.

Author contributions

A.N., A.V.G. and C.S undertook sample preparation, proteomics analysis, analyzed the omics data, prepared figures, and co-wrote the manuscript. A.K.A., A.M.D, H.K,, E.E., N.M.S, R.J.L, and L.K, were involved in collection of samples, biobanking, ethical approval, data management, study design, interpretation of results, and co-wrote the manuscript. SOM, L.K, J.E conceived the study, were involved in study design, data management and analysis, interpretation of results, supervision, and co-wrote the manuscript. All authors critically reviewed the manuscript and approved the final version for submission.

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Disclosures

This manuscript may be made available as a preprint on a recognized preprint server, prior to or during consideration for publication.

Data availability statement

Data and code are not publicly available because they contain sensitive patient information. Requests for access can be made directly to the FinnBrain Birth Cohort.

TABLE AND FIGURE LEGENDS

Table 1. Clinical characteristics of the FinnBrain placental sub-cohort. Participants were grouped by mean EPDS score, calculated from self-reported interviewer data collected at 14, 24, and 34 weeks' gestation, and categorised into three depressive symptom groups: low (0–4), moderate (5–9), and high (≥10). The table reports the following characteristics: infant sex, maternal age, maternal BMI, gestational diabetes, antidepressant use, smoking status, gestational age at delivery (days), mode of delivery (vaginal or caesarean section), and time from delivery to placental sample snap-freezing (minutes). Data are mostly register-based, supplemented by participant self-reporting.

Figure 1: Effect of Maternal Depression on the Proteomic Profile of Placental Tissue **(A)** Partial Least Squares Discriminant Analysis (PLS-DA) plot of the placental proteome in Low, Moderate, and High maternal depression groups. **(B)** Top 20 proteins ranked by Variable Importance in Projection (VIP) scores. **(C and D)** Volcano plots showing proteins associated with maternal depression in the Moderate and High depression groups (univariate GLM, nominal effect of Depression, $p < 0.05$). Log2 fold change is shown on the x-axis and −log10(p-value) from Tukey post hoc tests on the y-axis. Proteins are colour-coded according to statistical significance, and the strongest hits are annotated. Horizontal and vertical reference lines indicate Tukey-adjusted $p = 0.05$ and zero-fold change, respectively. **(E and F)** STRING pathway analysis identifying the molecular networks implicated in moderate and high depression, respectively.

Figure 2: Violin plots showing the nine shared proteins between moderate and high depression groups (ADH1C, BCAS2, GOLGA2, HSD3B2, LIMCH1, NUP188, NUP37, TRIM29, TXNDC5). All shared proteins were among the top 20 Variable Importance in Projection (VIP) features from the PLS-DA model (Figure 1B). * $p<0.05$ for Moderate vs Low or High vs Low depression groups (Tukey pairwise comparisons).

Figure 3: Differential expression analysis of proteins in male and female placentas across Low, Moderate, and High maternal depressive symptom groups. **(A-B)** Bar charts of proteins showing a main effect of Depression ($p<0.05$, two-way GLM) and concordant responses to maternal depression in male and female placentas. **(C-D)** Bar charts of proteins showing a significant Depression × Foetal Sex interaction ($p < 0.05$, two-way GLM) and divergent responses to depression in male and female placentas. Statistical details are provided in Tables S2 and S4.

Figure 4: Interaction-driven clustering of placental protein responses. Proteins showing a nominal interaction between maternal depression and foetal sex (unadjusted $p < 0.05$, two-way GLM) were subjected to unsupervised k-means clustering. **(A)** Heatmap showing six protein groups with similar response patterns, with rows ordered

by k-means cluster membership and columns hierarchically clustered. A diverging blue–white–red colour scale indicates relative decreases and increases in protein abundance in the Moderate and High depression symptom groups relative to Low symptom controls. **(B–E)** Enlarged heatmaps illustrating individual clusters 1, 6, 3, and 4, with annotated proteins. **(B) Cluster 1 (n=76):** The main processes identified were: ubiquitination, gene expression, cellular metabolism, vesicle-mediated transport, cellular organisation and cytoskeletal integrity, and cell polarity. **(C) Cluster 6 (n=23):** Proteins mapped to processes involving: protein synthesis and degradation, transport, secretion and signalling. **(D) Cluster 3 (n=13):** Proteins converged on biological processes mediating the lipid-autophagy axis, cell structure, adherence, invasion and proliferation. **(E) Cluster 4 (n=37):** Proteins in this cluster are related to complement and coagulation, inflammatory signalling, DNA repair, translation and transcription, vascular remodelling and cytoskeleton/extracellular matrix (ECM) (structural and membrane signalling).

TABLES

Table 1: Clinical characteristics of the FinnBrain placental sub-cohort

Demographics

Participant group: Average EPDS score (cumulative mean from RP 1,2,3)	**Maternal Depressive Symptoms (EPDS score)**		
	Low 0-4	**Moderate 5-9**	**High ≥10**
No. of mothers in each group	n=49	n=20	n=27
Sex of baby			
Male	27 (55.1%)	11 (55%)	16 (59.3%)
Female	22 (44.9%)	9 (45%)	11 (40.7%)
Maternal EPDS			
Mean	2.04	7.6	11.7
Median	2	8	11
Range	0-4	5-9	10-18
Maternal age			
Mean	31.08	28.8	31.89
Median	31	28.5	32
Range	21-41	21-38	19-38
Maternal BMI			
Mean	23.7	24.5	26.1
Median	22.7	22.8	24.6
Range	17.2-36.4	19.5-39.4	20.3-43.6
unknown	2	0	0
Overweight >25	9	5	13
Underweight <18.5	2	0	0
Gestational diabetes			
Yes	4 (8.5%)	0	4 (14.8%)
No	43 (91.5%)	20 (100%)	23 (85.2%)
Unknown	2	0	0
Antidepressant medication			
Yes	0	0	3
No	49	20	21
Unknown	0	0	3
Smoking status			
No	43	17	21
Stopped at 1st Trimester	2	3	4
Smoked after 1st Trimester	2	0	2
Unknown	2	0	0
Gestational age at delivery (Days)_infant			
Mean (days)	277	276.6	277
Median (days)	276	280	279
Range (days)	251-294	255-292	261-292

Mode of delivery			
Vaginal	**n=41 (87.2%)**	**n=16 (80%)**	**n=24 (88.9%)**
Vaginal	32	13	23
Breech presentation	3	0	0
Vacuum	6	3	1
Caesarean section	**n=6 (12.8%)**	**n=4 (20%)**	**n=3 (11.1%)**
Planned C-section	5	3	3
Unplanned C-section	1	1	0
Unknown	2	0	0
Time to freezing of placenta samples (mins)			
Mean	36.9	45.05	37.3
Median	36	50.5	35
Range	5-70	5-75	6-70

References

1. Álvarez-Mejía D, Rodas JA, Leon-Rojas JE (2025): From Womb to Mind: Prenatal Epigenetic Influences on Mental Health Disorders. *Int J Mol Sci* 26: 6096.

2. Ok L, Ohlund L, Inkster AM, Campbell KSJ, Peñaherrera MS, Brain U, *et al.* (2025): Effect of depression and serotonin reuptake inhibitors antidepressant treatment during pregnancy on protein expression in the human placenta: A quantitative proteomics analysis. *PLOS ONE* 20: e0322090.

3. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ (2010): A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction. *Archives of General Psychiatry* 67: 1012–1024.

4. Dadi AF, Miller ER, Bisetegn TA, Mwanri L (2020): Global burden of antenatal depression and its association with adverse birth outcomes: an umbrella review [no. 1]. *BMC Public Health* 20: 1–16.

5. Hannon S, Gartland D, Higgins A, Brown SJ, Carroll M, Begley C, Daly D (2022): Maternal mental health in the first year postpartum in a large Irish population cohort: the MAMMI study. *Arch Womens Ment Health* 25: 641–653.

6. Underwood L, Waldie K, D'Souza S, Peterson ER, Morton S (2016): A review of longitudinal studies on antenatal and postnatal depression. *Arch Womens Ment Health* 19: 711–720.

7. Lund RJ, Kyläniemi M, Pettersson N, Kaukonen R, Konki M, Scheinin NM, *et al.* (2021): Placental DNA methylation marks are associated with maternal depressive symptoms during early pregnancy. *Neurobiol Stress* 15: 100374.

8. Kirkpatrick M, Mandal G, Elhadidy I, Mariani N, Priestley K, Pariante CM, Borsini A (2025): From placenta to the foetus: a systematic review of in vitro models of stress- and inflammation-induced depression in pregnancy. *Mol Psychiatry* 30: 1689–1707.

9. Layton E, Mitchell AR, Kennedy E, Moran AC, Palestra F, Chowdhary N, *et al.* (2025): Maternal mental health matters: Indicators for perinatal mental health—A scoping review. *PLOS ONE* 20: e0317998.

10. Roddy Mitchell A, Gordon H, Lindquist A, Walker SP, Homer CSE, Middleton A, *et al.* (2023): Prevalence of Perinatal Depression in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *JAMA Psychiatry* 80: 425.

11. Field T (2011): Prenatal depression effects on early development: A review. *Infant Behavior and Development* 34: 1–14.

12. The Lancet (2023): Perinatal depression: a neglected aspect of maternal health. *The Lancet* 402: 667.

13. Amer SA, Zaitoun NA, Abdelsalam HA, Abbas A, Ramadan MS, Ayal HM, *et al.* (2024): Exploring predictors and prevalence of postpartum depression among mothers: Multinational study. *BMC Public Health* 24: 1308.

14. Karlsson L, Tolvanen M, Scheinin NM, Uusitupa H-M, Korja R, Ekholm E, *et al.* (2018): Cohort Profile: The FinnBrain Birth Cohort Study (FinnBrain). *International Journal of Epidemiology* 47: 15–16j.

15. Nugent BM, Bale TL (2015): The omniscient placenta: Metabolic and epigenetic regulation of fetal programming. *Frontiers in Neuroendocrinology* 39: 28–37.

16. Lacagnina S (2019): The Developmental Origins of Health and Disease (DOHaD). *Am J Lifestyle Med* 14: 47–50.

17. Kramer AC, Jansson T, Bale TL, Powell TL (2023): Maternal-fetal cross-talk via the placenta: influence on offspring development and metabolism. *Development* 150: dev202088.

18. Viuff AC, Sharp GC, Rai D, Henriksen TB, Pedersen LH, Kyng KJ, *et al.* (2018): Maternal depression during pregnancy and cord blood DNA methylation: findings from the Avon Longitudinal Study of Parents and Children. *Transl Psychiatry* 8: 244.

19. Drzymalla E, Gladish N, Koen N, Epstein MP, Kobor MS, Zar HJ, *et al.* (2021): Association between maternal depression during pregnancy and newborn DNA methylation. *Transl Psychiatry* 11: 572.

20. Abrishamcar S, Zhuang BC, Thomas M, Gladish N, MacIsaac JL, Jones MJ, *et al.* (2024): Association between maternal perinatal stress and depression and infant DNA methylation in the first year of life. *Transl Psychiatry* 14: 445.

21. Bronson SL, Chan JC, Bale TL (2017): Sex-Specific Neurodevelopmental Programming by Placental Insulin Receptors on Stress Reactivity and Sensorimotor Gating. *Biological Psychiatry* 82: 127–138.

22. Cissé YM, Montgomery KR, Zierden HC, Hill EM, Kane PJ, Huang W, *et al.* (2024): Maternal preconception stress produces sex-specific effects at the maternal:fetal interface to impact offspring development and phenotypic outcomes†. *Biology of Reproduction* 110: 339–354.

23. Musillo C, Ajmone-Cat MA, De Simone R, Tassinari R, Maranghi F, Tait S, *et al.* (2025): Maternal stressors disrupt mouse placental proteome and fetal brain development in a sex-specific fashion through inflammation and oxidative stress. *Mol Psychiatry* 30: 5072–5083.

24. Chan JC, Nugent BM, Bale TL (2018): Parental Advisory: Maternal and Paternal Stress Can Impact Offspring Neurodevelopment. *Biological Psychiatry* 83: 886–894.

25. Christians JK (2022): The Placenta's Role in Sexually Dimorphic Fetal Growth Strategies. *Reprod Sci* 29: 1895–1907.

26. Khorami Sarvestani S, Shojaeian S, Vanaki N, Ghresi-Fard B, Amini M, Gilany K, *et al.* (2021): Proteome profiling of human placenta reveals developmental stage-dependent alterations in protein signature. *Clin Proteomics* 18: 18.

27. Manna S, Scheel J, Noone A, McElwain CJ, Scaife C, Gupta S, *et al.* (2023): A proteomic profile of the healthy human placenta. *Clinical Proteomics* 20: 1.

28. Cox JL, Holden JM, Sagovsky R (1987): Detection of Postnatal Depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *The British Journal of Psychiatry* 150: 782–786.

29. Levis B, Negeri Z, Sun Y, Benedetti A, Thombs BD (2020): Accuracy of the Edinburgh Postnatal Depression Scale (EPDS) for screening to detect major depression among pregnant and postpartum women: systematic review and meta-analysis of individual participant data. *BMJ* m4022.

30. Miller ES, Saade GR, Simhan HN, Monk C, Haas DM, Silver RM, *et al.* (2022): Trajectories of antenatal depression and adverse pregnancy outcomes. *Am J Obstet Gynecol* 226: 108.e1-108.e9.

31. O'Connor LA, Melo TG, Golubeva AV, Donoso F, Scaife C, English JA, *et al.* (2025): Plasma proteomic signature of chronic psychosocial stress in mice. *Physiology & Behavior* 289: 114743.

745 32. Noone A, Dowling K, O'Boyle D, Carter M, Golubeva AV, Scaife C, *et al.* (2026):
746 Longitudinal multi-omics analysis of umbilical cord blood and childhood serum
747 in Autism. *Mol Psychiatry* 31: 701–713.
748 33. Tyanova S, Temu T, Cox J (2016): The MaxQuant computational platform for mass
749 spectrometry-based shotgun proteomics. *Nat Protoc* 11: 2301–2319.
750 34. Benjamini Y, Hochberg Y (1995): Controlling the False Discovery Rate: A Practical
751 and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical*
752 *Society Series B (Methodological)* 57: 289–300.
753 35. Szklarczyk D, Gable AL, Nastou KC, Lyon D, Kirsch R, Pyysalo S, *et al.* (2021): The
754 STRING database in 2021: customizable protein–protein networks, and
755 functional characterization of user-uploaded gene/measurement sets. *Nucleic*
756 *Acids Res* 49: D605–D612.
757 36. Karahoda R, Kallol S, Groessl M, Ontsouka E, Anderle P, Fluck C, *et al.* (2021):
758 Revisiting Steroidogenic Pathways in the Human Placenta and Primary Human
759 Trophoblast Cells. *Int J Mol Sci* 22: 1704.
760 37. Yokohama Y, Watanabe Y, Nakajima K, Umezawa A, Takahashi S, Mori Y, *et al.* (2026):
761 The Expression of Placental 17β-Hydroxysteroid Dehydrogenase Genes Is
762 Associated with the Elevation of Active Androgens and Estrogens in Pregnant
763 Women, but Does Not Affect 11-Oxygenated C19 Steroids. *International Journal*
764 *of Molecular Sciences* 27: 4290.
765 38. Chatuphonprasert W, Jarukamjorn K, Ellinger I (2018): Physiology and
766 Pathophysiology of Steroid Biosynthesis, Transport and Metabolism in the
767 Human Placenta. *Front Pharmacol* 9: 1027.

768 39. Parenti M, Schmidt RJ, Tancredi DJ, Hertz-Picciotto I, Walker CK, Slupsky CM (2024):
769 Neurodevelopment and Metabolism in the Maternal-Placental-Fetal Unit. *JAMA*
770 *Netw Open* 7: e2413399.
771 40. Baron-Cohen S, Tsompanidis A, Auyeung B, Nørgaard-Pedersen B, Hougaard DM,
772 Abdallah M, *et al.* (2020): Foetal oestrogens and autism [no. 11]. *Mol Psychiatry*
773 25: 2970–2978.
774 41. Yin H, Zhang J, Chen Y, Guo J, Li Q, Dinnyes A, *et al.* (2024): Placenta-specific
775 CYP11A1 overexpression lead to autism-like symptom in offspring with altered
776 steroid hormone biosynthesis in the placenta-brain axis and rescued by vitamin
777 D intervention. *Brain, Behavior, and Immunity* 121: 13–25.
778 42. Pan T, He G, Chen M, Bao C, Chen Y, Liu G, *et al.* (2017): Abnormal CYP11A1 gene
779 expression induces excessive autophagy, contributing to the pathogenesis of
780 preeclampsia. *Oncotarget* 8: 89824–89836.
781 43. Vacher C-M, Lacaille H, O'Reilly JJ, Salzbank J, Bakalar D, Sebaoui S, *et al.* (2021):
782 Placental endocrine function shapes cerebellar development and social
783 behavior. *Nat Neurosci* 24: 1392–1401.
784 44. Sayres L, Ji S, Diaz CR, Gumina D, Su E (2023): The role of extracellular matrix
785 proteins on placental angiogenesis in severe fetal growth restriction. *American*
786 *Journal of Obstetrics & Gynecology* 228: S69.
787 45. Soles A, Selimovic A, Sbrocco K, Ghannoum F, Hamel K, Moncada EL, *et al.* (2023):
788 Extracellular Matrix Regulation in Physiology and in Brain Disease. *Int J Mol Sci*
789 24: 7049.

790 46. Philosoph LK, Yoffe C, El Biri B, Baryakh P, Saar EG, Mayorov M, Yosef OB (2025):
791 Distinct protein profiles in cord blood plasma of children with autism spectrum
792 disorder. *Sci Rep* 15: 44947.
793 47. Rainville JR, Lipuma T, Hodes GE (2022): Translating the Transcriptome: Sex
794 Differences in the Mechanisms of Depression and Stress, Revisited. *Biological*
795 *Psychiatry* 91: 25–35.
796 48. Bucknor MC, Keating BA, Han VX, Gloss BS, Dey P, Aryamanesh N, *et al.* (2026):
797 Cumulative environmental exposures adversely impact social behaviour and are
798 associated with dysregulation of genes and proteins involved in epigenetic,
799 ribosomal, and immune regulation in male mice. *Inflamm Res* 75: 17.
800 49. Baines KJ, West RC (2023): Sex differences in innate and adaptive immunity impact
801 fetal, placental, and maternal health. *Biology of Reproduction* 109: 256–270.
802 50. Braun AE, Mitchel OR, Gonzalez TL, Sun T, Flowers AE, Pisarska MD, Winn VD (2022):
803 Sex at the interface: the origin and impact of sex differences in the developing
804 human placenta. *Biol Sex Differ* 13: 50.
805 51. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, *et al.* (2008):
806 Persistent epigenetic differences associated with prenatal exposure to famine in
807 humans. *Proc Natl Acad Sci U S A* 105: 17046–17049.
808 52. Wong G, Weir JM, Mishra P, Huynh K, Nijagal B, Gupta V, *et al.* (2021): The placental
809 lipidome of maternal antenatal depression predicts socio-emotional problems
810 in the offspring. *Transl Psychiatry* 11: 107.
811 53. Pellowski JA, Wedderburn CJ, Groenewold NA, Roos A, Subramoney S, Hoffman N,
812 *et al.* (2023): Maternal perinatal depression and child brain structure at 2-3 years
813 in a South African birth cohort study. *Transl Psychiatry* 13: 96.

814 54. Girchenko P, Lahti-Pulkkinen M, Laivuori H, Kajantie E, Räikkönen K (2025): Maternal
815 Antenatal Depression Is Associated With Metabolic Alterations That Predict Birth
816 Outcomes and Child Neurodevelopment and Mental Health. *Biological*
817 *Psychiatry* 97: 269–278.
818 55. Gurol-Urganci I, Langham J, Tassie E, Heslin M, Byford S, Davey A, *et al.* (2024):
819 Community perinatal mental health teams and associations with perinatal
820 mental health and obstetric and neonatal outcomes in pregnant women with a
821 history of secondary mental health care in England: a national population-based
822 cohort study. *The Lancet Psychiatry* 11: 174–182.
823 56. Curry et al. (2019): Interventions to Prevent Perinatal Depression: US Preventive
824 Services Task Force Recommendation Statement. *JAMA* 321: 580–587.
825 57. Huschke S, Murphy-Tighe S, Barry M (2020): Perinatal mental health in Ireland: A
826 scoping review. *Midwifery* 89: 102763.
827 58. Webb R, Ayers S, Shakespeare J (2022): Improving accessing to perinatal mental
828 health care. *Journal of Reproductive and Infant Psychology* 40: 435–438.
829 59. Hankin BL, Demers CH, Hennessey E-MP, Perzow SED, Curran MC, Gallop RJ, *et al.*
830 (2023): Effect of Brief Interpersonal Therapy on Depression During Pregnancy: A
831 Randomized Clinical Trial. *JAMA Psychiatry* 80: 539–547.
832 60. Talati A (2023): Maternal Depression, Prenatal SSRI Exposure, and Brain Trajectories
833 in Childhood. *JAMA Psychiatry* 80: 1191–1192.
834 61. Chan JKN, Zhong AHF, Lam JYH, Wong CSM, Solmi M, Correll CU, Chang WC (2026):
835 Maternal and paternal antidepressant use before and during pregnancy and
836 offspring risk of neurodevelopmental disorders: a systematic review and meta-
837 analysis. *The Lancet Psychiatry* 13: 472–484.

838

Figure 1

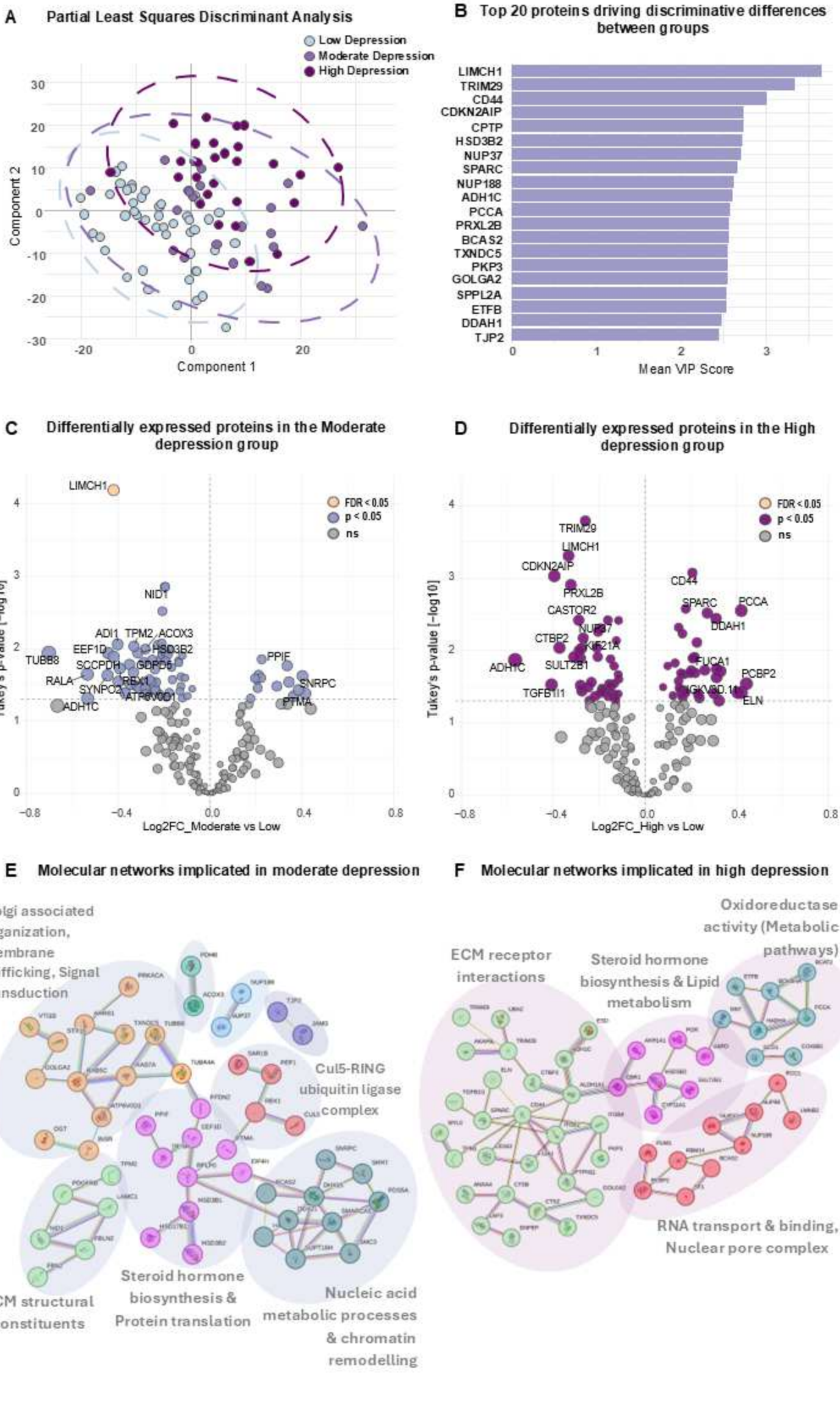

A
Partial Least Squares Discriminant Analysis
Low Depression
Moderate Depression
High Depression
Component 2
Component 1
B
Top 20 proteins driving discriminative differences between groups
LIMCH1
TRIM29
CD44
CDKN2AIP
CPTP
HSD3B2
NUP37
SPARC
NUP188
ADH1C
PCCA
PRXL2B
BCAS2
TXNDC5
PKP3
GOLGA2
SPPL2A
ETFB
DDAH1
TJP2
Mean VIP Score
C
Differentially expressed proteins in the Moderate depression group
FDR < 0.05
p < 0.05
ns
Tukey's p-value [−log10]
Log2FC_Moderate vs Low
D
Differentially expressed proteins in the High depression group
Log2FC_High vs Low
E
Molecular networks implicated in moderate depression
Golgi associated organization, Membrane trafficking, Signal transduction
Cul5-RING ubiquitin ligase complex
ECM structural constituents
Steroid hormone biosynthesis & Protein translation
Nucleic acid metabolic processes & chromatin remodelling
F
Molecular networks implicated in high depression
Oxidoreductase activity (Metabolic pathways)
ECM receptor interactions
Steroid hormone biosynthesis & Lipid metabolism
RNA transport & binding, Nuclear pore complex

Figure 2

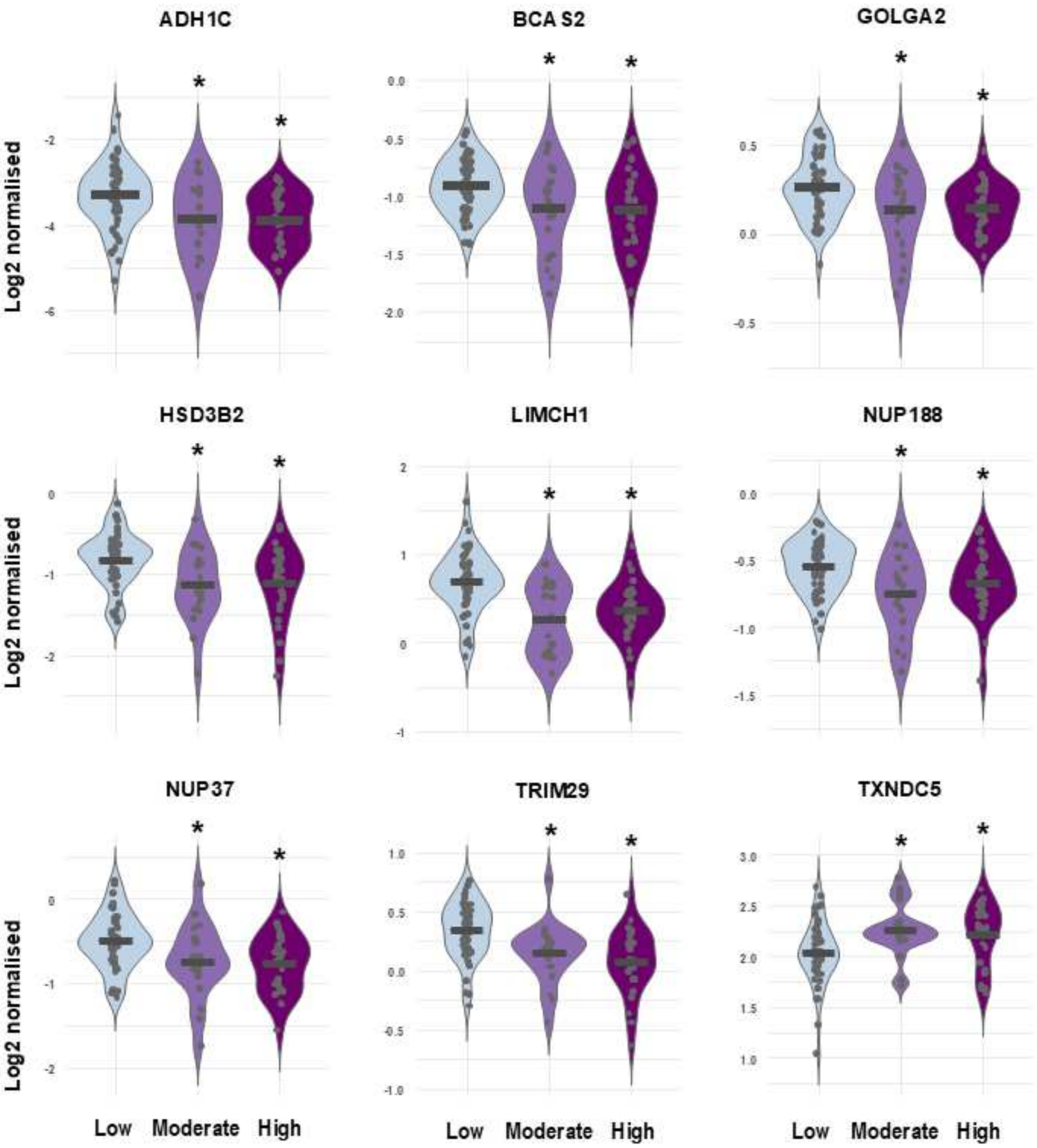

ADH1C
BCAS2
GOLGA2
HSD3B2
LIMCH1
NUP188
NUP37
TRIM29
TXNDC5
Log2 normalised
Low
Moderate
High
*

Figure 3

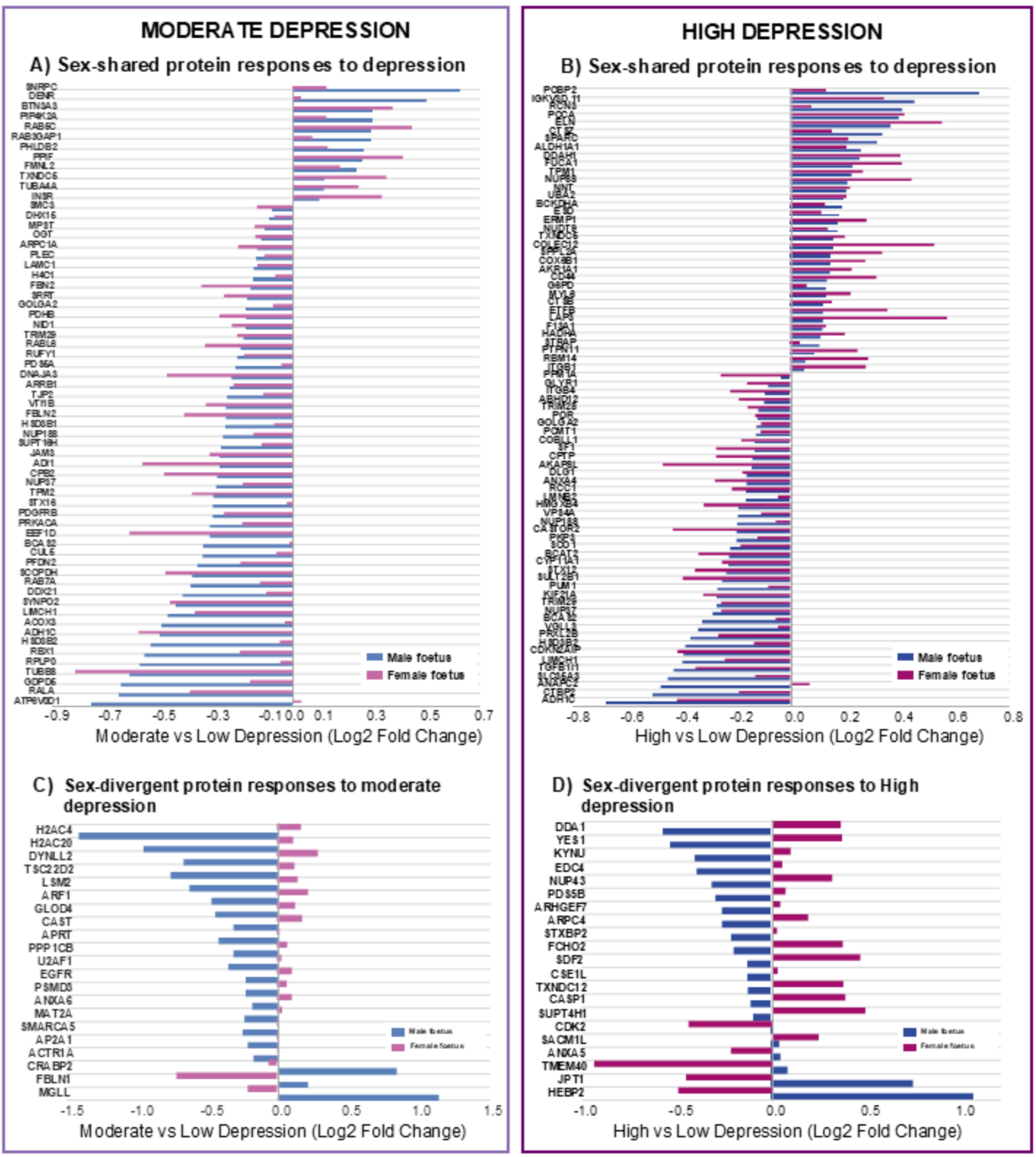
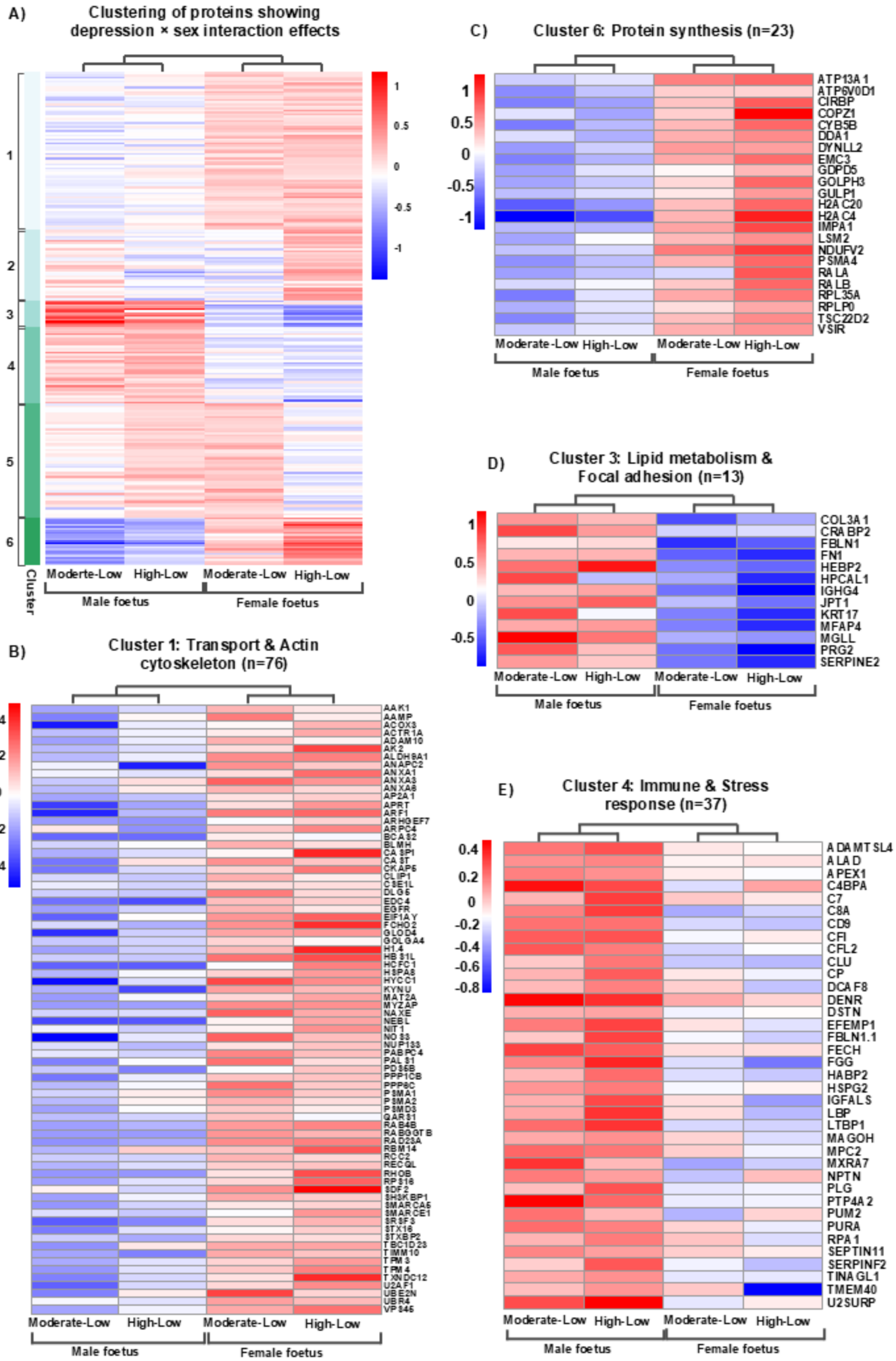

MODERATE DEPRESSION
A) Sex-shared protein responses to depression
SNRPC
DENR
BTN3A3
PIP4K2A
RAB5C
RAB30AP1
PHLDB2
PRIF
FMNL2
TXNDC5
TUBA4A
INSR
SMC3
DHX15
MPST
OGT
ARPC1A
PLEC
LAMC1
H4C1
FBN2
SRRT
GOLGA2
PDHB
NID1
TRIM28
RABL6
RUFY1
PDS5A
DNAJA3
ARRB1
TJP2
VTI1B
FBLN2
HSD3B1
NUP188
SUPT16H
JAM3
ADI1
CPB2
NUP37
TPM2
STX16
PDGFRB
PRKACA
EEF1D
BCAS2
CUL5
PFDN2
SCOPDH
RAB7A
DDX21
SYNPO2
LIMCH1
AOOX3
ADH1C
HSD3B2
RBX1
RPLP0
TUBB8
GDPD5
RALA
ATP6V0D1
Male foetus
Female foetus
-0.9 -0.7 -0.5 -0.3 -0.1 0.0 0.1 0.3 0.5 0.7
Moderate vs Low Depression (Log2 Fold Change)
HIGH DEPRESSION
B) Sex-shared protein responses to depression
POBP2
IGKV3D-11
RTN3
PDCA
ELN
CTIF
SPARD
ALDH1A1
DDAH1
FUCA1
TPM1
NUP88
NNT
UBA2
BCKDHA
E3BD
ERMP1
NUDT9
TXNDC5
COLEC12
SPRL2A
COX6B1
AKR1A1
CD44
G6PD
MYL9
C1QB
FTSJ3
LAP3
FTSJ1
HLCHA
STBAP
PTPN11
RBM14
ITGB1
PPM1A
GLYR1
ITGB4
ARHGDI2
TRIM25
PDIR
GOLGA2
PGMT1
COBLL1
BP1
CPTP
AKAP8L
DLGT
ANXA4
RCC1
LMNB2
HMGXB4
VPS4A
NUP188
CATSPS2
PKP3
SOD1
SCAT2
CYP11A1
STX12
SULT2B1
PUM1
KIF21A
TRIM29
NUP37
BCAS2
VCL L3
PRRL2B
HSD3B1
CDKN2A
LIMCH1
TGFB1I1
SLC35A2
ANXA5
CTBP2
ADH1C
Male foetus
Female foetus
-0.8 -0.6 -0.4 -0.2 0.0 0.2 0.4 0.6 0.8
High vs Low Depression (Log2 Fold Change)
C) Sex-divergent protein responses to moderate depression
H2AC4
H2AC20
DYNLL2
TSC22D2
LSM2
ARF1
GLOD4
CAST
APRT
PPP1CB
U2AF1
EGFR
PSMD8
ANXA6
MAT2A
SMARCA5
AP2A1
ACTR1A
CRABP2
FBLN1
MGLL
Male foetus
Female foetus
-1.5 -1.0 -0.5 0.0 0.5 1.0 1.5
Moderate vs Low Depression (Log2 Fold Change)
D) Sex-divergent protein responses to High depression
DDA1
YES1
KYNU
EDC4
NUP43
PDS5B
ARHGEF7
ARPC4
STXBP2
FCHO2
SDF2
CSE1L
TXNDC12
CASP1
SUPT4H1
CDK2
SACM1L
ANXA5
TMEM40
JPT1
HEBP2
Male foetus
Female foetus
-1.0 -0.5 0.0 0.5 1.0
High vs Low Depression (Log2 Fold Change)

Figure 4


A)
Clustering of proteins showing depression × sex interaction effects
Cluster
Moderte-Low
High-Low
Moderate-Low
High-Low
Male foetus
Female foetus
B)
Cluster 1: Transport & Actin cytoskeleton (n=76)
C)
Cluster 6: Protein synthesis (n=23)
ATP13A1
ATP6V0D1
CIRBP
COPZ1
CYB5B
DDA1
DYNLL2
EMC3
GDPD5
GOLPH3
GULP1
H2AC20
H2AC4
IMPA1
LSM2
NDUFV2
PSMA4
RALA
RALB
RPL35A
RPLP0
TSC22D2
VSIR
D)
Cluster 3: Lipid metabolism & Focal adhesion (n=13)
COL3A1
CRABP2
FBLN1
FN1
HEBP2
HPCAL1
IGHG4
JPT1
KRT17
MFAP4
MGLL
PRG2
SERPINE2
E)
Cluster 4: Immune & Stress response (n=37)
ADAMTSL4
ALAD
APEX1
C4BPA
C7
C8A
CD9
CFI
CFL2
CLU
CP
DCAF8
DENR
DSTN
EFEMP1
FBLN1.1
FECH
FGG
HABP2
HSPG2
IGFALS
LBP
LTBP1
MAGOH
MPC2
MXRA7
NPTN
PLG
PTP4A2
PUM2
PURA
RPA1
SEPTIN11
SERPINF2
TINAGL1
TMEM40
U2SURP

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FinnBrainTableS2EffectofDepressionUnivariateGLMwithTukeyscomparisonsSignificanteffectofDepression.xlsx
- FinnBrainTableS1EffectofDepressionUnivariateGLMwithTukeyspairwiseposthoccomparisonsAllproteins.xlsx
- FinnBrainTableS4EffectofDepressionandFetalSexMultivatiateGLMwithTukeysEffectofDepressionandInteraction.xlsx
- FinnBrainTableS3EffectofDepressionandFetalSexMultivatiateGLMwithTukeyspairwiseposthoccomparisonsAllproteins.xlsx