



Disgust sensitivity is negatively associated with immune system activity in early pregnancy: Direct support for the Compensatory Prophylaxis Hypothesis

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ABSTRACT

According to the Compensatory Prophylaxis Hypothesis (CPH), disgust may be considered a part of the behavioral immune system, adjusting as a function of immunocompetence. Early pregnancy involves modulation of a complex network of various immune-related factors, but only a few studies so far have focused on disgust sensitivity in pregnant women in the context of the CPH. This study aimed to examine associations between disgust sensitivity and immune activity indices, cytokine levels, and white blood cell (WBC) count in pregnant women. The sample included 78 women in the 1st trimester of pregnancy. Higher disgust sensitivity (Disgust Scale-Revised; DS-R) was significantly associated with decreased levels of IL-1 β , IL-2, IL-4, IL-7, IL-17, Eotaxin, MCP-1 (MCAF), and RANTES in blood serum. This model explained 17.5% of the total DS-R score variability. Using the DS-R subscales, the Contamination disgust was significantly associated with levels of FGF basic, IFN- γ , IL-1 β , IL-2, IL-4, IL-7, IL-17A, G-CSF, MCP-1 (MCAF), MIP-1 α , PDGF-BB, and RANTES, and the Core disgust was significantly associated with levels of IL-1 β , IL-2, IL-4, IL-7, IL-17A, Eotaxin, G-CSF, IP-10, MCP-1 (MCAF), PDGF-BB, and TNF- α . Disgust sensitivity was not associated with WBC count. Disgust may reflect and compensate for insufficient immune adaptation in early pregnancy, suggesting the potential clinical significance of this common prenatal symptom.

1. Introduction

In the history of evolution, the need for protection against pathogens shaped not only individuals' physiology but also emotions and behavior (Aarøe, Osmundsen, & Petersen, 2016; Sarabian, Curtis, & McMullan, 2018). It is assumed that apart from the physiological immune system defending an organism against infections, individuals also developed a behavioral immune system that operates, at least partially, through the emotion of disgust (Curtis, Aunger, & Rabie, 2004; Sarabian, Belais, & MacIntosh, 2021). Disgust seems to be elicited when the individual

encounters potentially harmful substances, thus facilitating avoidance of pathogens that could cause disease (Curtis et al., 2004). As such, disgust has been conceptualized as a disease-avoidance mechanism (Oaten, Stevenson, & Case, 2009). Moreover, disgust may function not only as a mere complement to the physiological immune system. According to the Compensatory Prophylaxis Hypothesis (CPH) proposed by Fessler, Eng, and Navarrete (2005), disgust can also compensate for the decline in physiological immunity, adjusting as a function of immunocompetence.

Fessler et al. (2005) tested the adaptive function of disgust in

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pregnancy and found an increased disgust sensitivity in the first trimester compared to the later stages of pregnancy. As the then understanding was that early pregnancy is a state of substantial immune suppression to tolerate the semi-allogenic fetus, the authors (Fessler et al., 2005) interpreted those results in favor of the CPH, presuming that disgust compensates for the expected decrease in immune response in early pregnancy. Nevertheless, recent evidence suggests that the view of early pregnancy as a state of reduced immunocompetence is outdated: the immune system has been shown to be highly functional and active in the initial phase of pregnancy, producing a strong immune response when facing a risk of infection (Racicot, Kwon, Aldo, Silasi, & Mor, 2014). Some immune responses are indeed suppressed during pregnancy (i.e., lymphocytes decline) to tolerate the semi-allogenic fetus (Hové et al., 2020), however, others (such as inflammatory processes) are elevated, suggesting that pregnancy is a state of a complex and dynamic immune-modulation that decreases the risk of fetal exposure to pathogens but at the same time limits immune rejection of the fetus.

There is indeed evidence of elevated concentrations of pro-inflammatory cytokines, small proteins with pleiotropic functions, in the first trimester of pregnancy (Stokkeland et al., 2019). Higher pro-inflammatory cytokine levels at this stage of pregnancy indicate that inflammation is required for successful blastocyst implantation (Mor, Cardenas, Abrahams, & Guller, 2011). Nevertheless, the recent multiparameter studies, including simultaneous cellular, transcriptomic and proteomic approaches, provide a more detailed picture of immune adaptation in pregnancy, indicating that early pregnancy is a state of activation of a more complex network of various immune-related factors rather than a state of increased inflammation specifically (Peterson et al., 2020; Sharma, Godbole, & Modi, 2016). While processes of implantation and placental development are associated with an increase of pro-inflammatory cytokine levels (e.g. IL-2, IL-6, IL-8, IL-15, IL-17, TNF- α , IFN- γ), maternal immune response to inflammation involves a production of regulatory and anti-inflammatory mediators (e.g. IL-1ra, IL-4, and IL-9) (Curry et al., 2008; Jarmund et al., 2021; Mor et al., 2011; PrabhuDas et al., 2015; Spence et al., 2021). Following these recent perspectives, disgust sensitivity in early pregnancy can no longer be viewed simply as a mechanism compensating for the putative decline in the immune response, but rather as a mechanism compensating for insufficient immune adaptation, i.e., for a failure to establish the immune environment protective for both the mother and the fetus.

Although research related to the CPH has expanded in recent years, the adaptive function of disgust in pregnancy remains an understudied area of research. So far, only two studies have focused on disgust in pregnant women in the context of the CPH, reporting the changes in disgust sensitivity across pregnancy and linking them to the presumed immune alterations (Fessler et al., 2005; Zelazniewicz & Pawlowski, 2015), though no study associated disgust sensitivity in pregnancy with immune factors directly. Nevertheless, examining the direct link between disgust sensitivity and immune system functioning is of great clinical relevance as high disgust sensitivity might serve as a marker of suboptimal immune system functioning that could be detected as soon as in early pregnancy. Importantly, optimal immune system activity is essential for successful pregnancy outcomes (Mor et al., 2011; Peterson et al., 2020), with dysregulation of immune adaptation potentially leading to the development of a spectrum of pregnancy complications with further implications for placental and fetal development (Arck & Hecher, 2013).

The aim of this study was to examine the associations between disgust sensitivity and maternal immune activity indices (cytokine levels and white blood cell count) in the first trimester of pregnancy. As there is evidence suggesting complex immune activity in early pregnancy, we assessed the levels of a wide range of mediators, including pro-inflammatory cytokines (IL-6, GM-CSF, IL-1 β , TNF- α), Th1 (IFN- γ , IL-12, IL-2), Th2 (IL-4, IL-5, IL-9, IL-13), Th17 (IL-17A, IL-15), anti-inflammatory cytokines (IL-1ra, IL-10), chemokines (MCP-1, MIP-1 α , MIP-1 β , RANTES, Eotaxin, IP-10) and growth factors (FGF basic, G-CSF, IL-7,

PDGF-BB VEGF). This approach enabled us to establish a more integrated perspective on the association between disgust sensitivity and immune functioning. We also considered nausea and vomiting in pregnancy (NVP) in our analyses because there is a close association between disgust and pregnancy sickness. We hypothesized that higher disgust sensitivity would be associated with lower concentrations of maternal serum cytokines and lower white blood cell (WBC) count. Similarly, we expected that more severe NVP would be associated with lower concentrations of maternal serum cytokines and lower WBC count.

2. Material and methods

2.1. Participants

The sample consisted of 78 women aged 22–41 years (mean age = 32.2, SD = 4.4). Out of those women, 42 (53.8%) were primiparas, and 31 (39.7%) were primiparas without a history of abortion or miscarriage. Ten women (12.8%) became pregnant after fertility treatment, of which two women through intrauterine insemination (IUI) and eight women through in vitro fertilization (IVF). A majority of the women (56; 71.8%) had a university degree, while 21 (26.9%) had secondary education and one woman (1.3%) had elementary education. Forty-two (53.8%) women were bearing a male fetus (data concerning child sex were extracted from medical records after the child's birth). The participating women were generally healthy, without serious health complications before and during pregnancy.

2.2. Procedures

This study is a part of a larger prospective longitudinal project focusing on maternal emotional status in pregnancy and its biological correlates. This project commenced in June 2018 in collaboration with a private gynecological clinic located in Prague, Czech Republic. Pregnant women were recruited between the 4th and 12th week of pregnancy (T1) (mean = 7.5, SD = 1.5) during their antenatal medical check-up at the clinic. They completed a background questionnaire and questionnaires related to disgust sensitivity and nausea and vomiting at the time of recruitment. Blood samples for determining cytokine levels and white blood cell (WBC) count were collected during the medical check-up between the 9th and 14th week of pregnancy (T2) (mean = 10.3, SD = 0.9). Data related to WBC count were extracted from medical records ($N = 77$; for WBC count parameters, see the electronic supplementary material, Table S1). The laboratory analyses were carried out at the Institute of Endocrinology in Prague. All participating women provided written informed consent. This research project has been approved by the Institutional Review Board of the Faculty of Science, Charles University (Approval No. 2018/6 and 2019/10).

2.3. Questionnaires

Disgust sensitivity was assessed by the Disgust Scale-Revised (DS-R) (Olatunji et al., 2007). DS-R is a self-report scale consisting of three subscales: Core disgust (elicited by food, animal, and body products), Animal-reminder disgust (related to what reminds us of our own mortality, to an injury to the body or a violation of outer bodily envelope), and Contamination disgust (concerns about interpersonal transmission of pathogens). DS-R contains 25 items. The Core disgust subscale consists of 12 items, the Animal-reminder disgust subscale of 8 items, and the Contamination disgust subscale of 5 items. The items are rated on a 5-point scale ranging from 0 to 4. The overall score may range from 0 to 100, with a higher score indicating greater disgust sensitivity. Incomplete questionnaires (with over one-fifth of each domain or questionnaire unanswered) were excluded from the analyses ($N = 1$). If one fifth or fewer responses in each domain were missing, we used the average score in the corresponding domain to supplement these missing values ($N = 2$, in both cases, one answer was replaced). DS-R showed high

reliability (Cronbach's alpha = 0.843), however, the subscales' reliability was somewhat lower: 0.61 for Core disgust, 0.76 for Animal-reminder disgust, and 0.57 for Contamination disgust. The mean overall DS-R score ($N = 77$) was 51.2 (SD = 14.9); the mean score on the Core disgust subscale was 26.2 (SD = 6.7), on the Animal-reminder disgust subscale 16.3 (SD = 6.4) and on the Contamination disgust subscale 8.0 (SD = 3.4).

The levels of nausea and vomiting in pregnancy (NVP) were assessed using the Index of Nausea, Vomiting, and Retching (INVR) (Rhodes & McDaniel, 1999), an instrument that was previously used in the population of pregnant women (Fiurášková, Havlíček, & Roberts, 2021; Koken et al., 2008). INVR consists of 8 items focusing on symptoms that occurred in the last 12 h. There are five possible responses to each question (ranging from 0 to 4). The overall score (i.e., Rhodes Index) may range from 0 to 32, with a higher score indicating greater symptom severity. In our sample, the mean score on Rhodes Index was 7.34 ($N = 73$; SD = 6.4). INVR showed high reliability (Cronbach's alpha = 0.843).

2.4. Cytokine analysis

Blood samples of 78 women in the 1st trimester of pregnancy were analyzed for cytokine concentrations in blood serum using multiplex bead-based suspension array system (xMAP technology, Luminex Corp.) with the Bio-Plex Pro Human Cytokine 27-Plex panel (Cat. No.: M500KCAF0Y, Bio-Rad) containing FGF basic, Eotaxin, G-CSF, GM-CSF, IFN- γ , IL-1 β , IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17A, IP-10, MCP-1 (MCAF), MIP-1 α , MIP-1 β , PDGF-BB, RANTES, TNF- α , VEGF under the standard protocol (for cytokine parameters see the Supplementary material, Table S1). All samples were run on a single plate. Data were evaluated by 5-parameter logistic regression with Bio-Plex Manager v. 6.1.1 (Bio-Rad). In some blood samples, some cytokines levels were below the detection limit of the laboratory method: FGF-basic ($N = 2$), GM-CSF ($N = 44$), IL-1 β ($N = 8$), IL-2 ($N = 21$), IL-5 ($N = 53$), IL-6 ($N = 71$), IL-7 ($N = 1$), IL-8, ($N = 47$), IL-10 ($N = 67$), IL-12 ($N = 74$), IL-13 ($N = 41$), IL-15 ($N = 76$), VEGF ($N = 55$). In some blood samples, some cytokine levels were above the detection limit of the laboratory method: RANTES ($N = 9$). Nine cytokines (IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, GM-CSF, and VEGF) with more than half of the levels below the detection limit of the laboratory method were not included in the final statistical analysis. If less than half of the values of the cytokine levels were below or above the limit of the laboratory method, we used the measured values out of limit that were available (for FGF-basic, $N = 2$; IL-1 β , $N = 8$; IL-2, $N = 21$; IL-7, $N = 1$; RANTES, $N = 9$).

2.5. Statistics

As preliminary analyses, we assessed an association between gestational age at T1 (questionnaire completing) and disgust sensitivity or NVP scores, and between gestational age at T2 (blood draws) and cytokines levels/WBC count, using the partial Kendall correlation and controlling for maternal age. The partial Kendall correlation controlling for maternal age and gestational age at T1 and T2 was used to assess the associations between disgust sensitivity (overall DS-R score and its subscales) or NVP (Rhodes Index) and cytokine levels/WBC count. A correction for multiple tests was applied using the Benjamini-Hochberg procedure with a false discovery rate pre-set to 0.1 (Benjamini & Hochberg, 1995). The statistical analyses were performed using R, version 3.5.1. (R Core Team, 2018), package ppcor v. 1.1 (Kim, 2015).

Multivariate regression with a reduction of dimensionality known as orthogonal projections to latent structures (OPLS) (Trygg & Wold, 2002) was conducted to further assess associations between disgust sensitivity or NVP and cytokine levels/WBC count. The OPLS model searches for the best linear combination of predictors for an optimum estimate of the dependent variable. Statistical software SIMCA v. 12.1.1.1. (Umetrics, Umea, Sweden) was used for the OPLS analysis. In the input models, we

included maternal age, maternal BMI before pregnancy (calculated based on a maternal report on her pre-pregnancy weight and height), gestational age at T1 and T2 (in days), method of conception (0: natural conception, 1: became pregnant after fertility treatment), parity (0: primipara, 1: multipara), and fetal sex (0: female, 1: male) as predictors. Before conducting the final statistical analyses, all variables, except for the binary, were transformed towards symmetric distribution and constant variance using STATGRAPHICS Centurion 18 software (The Plains, VA, USA). The values of all variables including cytokines were transformed by power transformations to attain symmetric data distribution and homoscedasticity; the transformed data were automatically converted to z-scores by SIMCA software for further analyses.

3. Results

A total of 77 pregnant women were included in the analyses addressing the associations between disgust sensitivity and immune markers, while 73 pregnant women were included in the analyses of the associations between nausea and vomiting (NVP) and immune markers. Levels of 18 cytokines were included in the final analyses.

3.1. Preliminary analyses

We observed no significant association between gestational age at the time of blood sampling (T2) and cytokine levels. However, our data showed a significant positive association between gestational age at the time of questionnaire completing (T1) and the overall DS-R score (Tau = 0.173, $P = 0.027$, Cohen's $d = 0.55$), the subscale Core disgust score (Tau = 0.191, $P = 0.015$, Cohen's $d = 0.61$), but not the subscales Animal-reminder disgust (Tau = 0.150, $P = 0.056$, Cohen's $d = 0.48$) and Contamination disgust scores (Tau = 0.086, $P = 0.270$, Cohen's $d = 0.28$). No significant association was found between gestational age at T1 and NVP (Tau = 0.130, $P = 0.106$, Cohen's $d = 0.42$).

As the next step, we examined the associations between disgust (the overall DS-R score and three DS-R subscales) and cytokine levels/white blood cells (WBC) count in pregnancy using the partial Kendall correlation controlling for maternal age and gestational age at T1 and T2 (Table 1). After correction for multiple tests, we found significant negative correlations between the overall DS-R score and the following cytokines (but not WBC count): Eotaxin, IL-1 β , IL-2, IL-4, IL-7, IL-17A, and MCP-1. As for the DS-R subscales, we found significant negative correlations between the Core disgust score and Eotaxin, IL-4, IL-7, and IL-17A, but not WBC count; and between the Contamination disgust score and FGF basic, IFN- γ , IL-1 β , IL-2, IL-4, IL-7, IL-17A, MCP-1, PDGF-BB, RANTES, and WBC count. No significant associations were detected between the Animal-reminder disgust score and cytokine levels/WBC count. We also examined associations between nausea and vomiting in pregnancy (NVP) and cytokine levels or WBC count using the partial Kendall correlation controlling for maternal age and gestational age at T1 and T2 (Table 1). After correction for multiple tests, our results show no significant correlation between NVP and cytokines/WBC count.

3.2. Main analyses

We employed the multivariate OPLS models to evaluate associations between the disgust sensitivity representing vector Y , and the cytokine levels, WBC count, and related variables (maternal age, maternal BMI before pregnancy, gestational age at T1 and T2, method of conception, parity, and fetal sex) constituting matrix X . Separate OPLS models were developed for the overall DS-R score and the individual DS-R subscales. By using this approach, one predictive component was extracted for each model.

In the model for the overall DS-R score, disgust was significantly predicted by IL-1 β , IL-2, IL-4, IL-7, IL-17, Eotaxin, MCP-1 (MCAF), and RANTES, such that lower levels of cytokines predicted higher DS-R scores, but not by WBC count. This model explained 17.5% (after the

Table 1
Partial Kendall correlation between cytokines/WBC count and disgust sensitivity and nausea and vomiting.

	DS-R score			Core disgust			Animal-reminder disgust			Contamination disgust			Nausea and vomiting (Rhodes Index)				
	N	Kend τ	P-value	Coh d	Kend τ	P-value	Coh d	Kend τ	P-value	Coh d	Kend τ	P-value	Coh d	N	Kend τ	P-value	Coh d
FGF basic	77	-0.12	0.135	0.38	-0.07	0.412	0.22	-0.06	0.429	0.19	-0.17	0.028*	0.54	73	-0.04	0.630	0.13
Eotaxin	77	-0.18	0.021*	0.58	-0.20	0.011*	0.64	-0.10	0.206	0.32	-0.13	0.108	0.42	73	-0.12	0.160	0.38
G-CSF	77	-0.07	0.396	0.22	-0.09	0.278	0.29	0.03	0.703	0.10	-0.11	0.181	0.35	73	-0.08	0.343	0.26
IFN-γ	77	-0.12	0.128	0.38	-0.06	0.445	0.19	-0.08	0.296	0.26	-0.19	0.018*	0.61	73	0.03	0.719	0.10
IL-1β	77	-0.18	0.021*	0.58	-0.15	0.054	0.48	-0.07	0.370	0.22	-0.24	0.002*	0.77	73	-0.12	0.152	0.38
IL-1ra	77	0.00	0.980	0.00	0.03	0.732	0.10	-0.01	0.932	0.03	-0.06	0.436	0.19	73	-0.04	0.599	0.13
IL-2	77	-0.19	0.018*	0.61	-0.14	0.071	0.45	-0.12	0.122	0.38	-0.19	0.020*	0.61	73	-0.07	0.409	0.22
IL-4	77	-0.20	0.013*	0.64	-0.19	0.016*	0.61	-0.11	0.152	0.35	-0.17	0.034*	0.54	73	-0.09	0.252	0.29
IL-7	77	-0.18	0.021*	0.58	-0.20	0.012*	0.64	-0.07	0.411	0.22	-0.22	0.007*	0.70	73	-0.06	0.441	0.19
IL-9	77	0.06	0.457	0.19	0.08	0.289	0.26	0.04	0.608	0.13	0.05	0.509	0.16	73	-0.16	0.054	0.51
IL-17A	77	-0.20	0.014*	0.64	-0.21	0.010*	0.67	-0.09	0.236	0.29	-0.15	0.054 [†]	0.48	73	-0.07	0.398	0.22
IP10	77	-0.13	0.104	0.42	-0.17	0.035	0.54	-0.11	0.154	0.35	-0.07	0.374	0.22	73	-0.05	0.553	0.16
MCP-1 (MCAF)	77	-0.17	0.030*	0.54	-0.17	0.037	0.54	-0.12	0.135	0.38	-0.19	0.016*	0.61	73	-0.14	0.089	0.45
MIP-1α	77	-0.07	0.359	0.22	-0.08	0.311	0.26	-0.03	0.711	0.10	-0.12	0.142	0.38	73	-0.08	0.326	0.26
MIP-1β	77	-0.01	0.944	0.03	-0.03	0.696	0.10	0.04	0.646	0.13	-0.03	0.757	0.10	73	-0.08	0.314	0.26
PDGF-BB	77	-0.16	0.050	0.51	-0.11	0.159	0.35	-0.11	0.162	0.35	-0.21	0.007*	0.67	73	-0.12	0.140	0.38
RANTES	77	-0.15	0.056	0.48	-0.15	0.054	0.48	-0.10	0.232	0.32	-0.18	0.022*	0.58	73	-0.18	0.031	0.58
TNF-α	77	-0.08	0.310	0.26	-0.04	0.618	0.13	-0.05	0.553	0.16	-0.12	0.126	0.38	73	-0.13	0.124	0.42
WBC count	76	0.14	0.084	0.45	0.12	0.124	0.38	0.08	0.343	0.26	0.18	0.029*	0.58	73	0.13	0.121	0.42

Values in bold are significant ($P < 0.05$) before the correction for multiple tests. Results that remained significant after the correction for multiple tests. Adjusted for maternal gestational age at T1 and T2.
Kend τ = partial Kendall τ.
Coh d = Cohen's d.

cross-validation 15.2%) of the total DS-R scores variability (Table 2). The model for the subscale Contamination disgust revealed that higher subscale scores were predicted by lower levels of the following cytokines: FGF basic, IFN-γ, IL-1β, IL-2, IL-4, IL-7, IL-17A, G-CSF, MCP-1 (MCAF), MIP-1α, PDGF-BB, and RANTES. Again, the WBC count had no effect. As for the covariates, only the conception method contributed to the explanation of the Contamination disgust scores variability. This model explained 14.1% (after the cross-validation 10.0%) of this subscale scores variability (Table 3). The model for the subscale Core disgust revealed that this subscale scores were negatively associated with the following cytokines: TNF-α, IL-1β, IL-2, IL-4, IL-7, IL-17A, Eotaxin, G-CSF, IP-10, MCP-1 (MCAF), and PDGF-BB. This model explained 13.1% (after the cross-validation 8.9%) of this subscale scores variability (Table 3). The model for the subscale Animal-reminder disgust showed no significant associations between this subscale scores and cytokine levels or WBC count (Table 3).

As for the NVP, the OPLS model showed that NVP is significantly negatively associated with concentrations of IL-1β, IL-2, IL-4, IL-9, IL-17A, Eotaxin, G-CSF, MCP-1 (MCAF), PDGF-BB, RANTES, and TNF-α. In addition, NVP was significantly predicted by maternal age, such that the younger the mother, the higher the score on the NVP, an effect that was not confounded by parity. The model for NVP explained 11.5% (9% after

the cross-validation) of the variability of NVP scores (Table 4).

4. Discussion

The aim of this study was to test the Compensatory Prophylaxis Hypothesis (CPH) by examining the associations between disgust sensitivity and immune indices in early pregnancy. We observed that elevated disgust sensitivity (the total DS-R score) was significantly associated with decreased levels of a wide range of cytokines (the model for the total DS-R score explained 17.5% of data variability). Out of the individual DS-R subscales, the Contamination and Core disgust were significantly associated with cytokine levels (a total of 14.1% and 13.1% of the data variability were explained in the models, respectively). By linking higher disgust sensitivity with lower cytokine levels in pregnant women, this study is first to indicate that disgust sensitivity may compensate for insufficient immune functioning in early pregnancy.

4.1. Pregnancy as a state of complex immune adaptation

Pregnancy was considered a state of immune suppression within the classical paradigm. However, despite the fact that some immune responses are suppressed to tolerate the semi-allogenic fetus (Hové et al.,

Table 2
Relationships between DS-R score and predictors as evaluated by OPLS model and multiple regression (for details see Statistical analysis).

	Variable	OPLS, Predictive component			Multiple regression	
		Component loading	t-statistics	R ^a	Regression coefficient	t-statistics
Relevant predictors (matrix X)	IL-1β	-0.363	-14.65	-0.852**	-0.060	-3.36**
	IL-2	-0.347	-17.50	-0.815**	-0.065	-6.36**
	IL-4	-0.400	-20.07	-0.938**	-0.067	-4.16**
	IL-7	-0.355	-12.33	-0.833**	-0.062	-4.73**
	IL-17A	-0.365	-27.07	-0.856**	-0.063	-4.69**
	Eotaxin	-0.378	-13.43	-0.887**	-0.055	-2.76*
	MCP-1	-0.337	-8.71	-0.791**	-0.073	-4.80**
	RANTES	-0.290	-13.61	-0.680**	-0.057	-3.25**
	(matrix Y)	DS-R score	1.000	2.57	0.418*	
	Explained variability		17.5% (15.2% after cross-validation)			

^a R - component loadings expressed as correlation coefficients with predictive component. * $P < 0.05$. ** $P < 0.01$.

Table 3

Associations between DS-R subscales (Contamination disgust, Core disgust, Animal-reminder disgust) and predictors evaluated by OPLS model and multiple regression (for details see Statistical analysis).

	Variable	OPLS, Predictive component			Multiple regression		
		Component loading	t-statistics	R	Regression coefficient	t-statistics	
Relevant predictors (matrix X)	Method of conception	0.143	2.05	0.210*	0.043	2.56*	
	WBC count	-0.008	-0.12	0.200	0.040	1.57	
	IL-1β	-0.340	-26.07	0.039**	-0.053	-4.55**	
	IL-2	-0.336	-12.27	0.082**	-0.040	-4.49**	
	IL-4	-0.352	-13.95	0.076**	-0.040	-2.25*	
	IL-7	-0.324	-6.74	0.144**	-0.050	-3.95**	
	IL-17A	-0.326	-10.09	0.097**	-0.035	-2.00*	
	FGF basic	-0.280	-8.33	0.101**	-0.029	-2.93*	
	G-CSF	-0.311	-12.45	0.075**	-0.026	-2.28*	
	IFN-γ	-0.281	-8.48	0.099**	-0.041	-2.98*	
	MCP-1	-0.317	-14.98	0.064**	-0.045	-8.50**	
	MIP-1α	-0.273	-4.40	0.128**	-0.029	-2.91*	
	PDGF-BB	-0.240	-8.00	0.090**	-0.043	-3.09**	
	RANTES	-0.290	-6.55	0.133**	-0.038	-2.40*	
	(matrix Y)	Contamination disgust	1.000	4.80	0.624**		
	Explained variability		14.1% (10.0% after cross-validation)				
	Relevant predictors (matrix X)	IL-1β	-0.326	-20.06	-0.833**	-0.044	-2.20*
IL-2		-0.323	-11.26	-0.825**	-0.045	-3.23**	
IL-4		-0.366	-25.87	-0.935**	-0.049	-2.75*	
IL-7		-0.333	-9.31	-0.850**	-0.049	-3.07**	
IL-17A		-0.338	-9.74	-0.863**	-0.048	-3.04**	
Eotaxin		-0.350	-22.89	-0.893**	-0.044	-2.27*	
G-CSF		-0.318	-21.50	-0.812**	-0.026	-1.55	
IP-10		-0.194	-4.36	-0.495**	-0.047	-3.52**	
MCP-1		-0.303	-9.64	-0.774**	-0.048	-5.32**	
PDGF-BB		-0.220	-8.02	-0.562**	-0.033	-2.46*	
TNF-α		-0.284	-9.19	-0.726**	-0.027	-1.88	
(matrix Y)		Core disgust	1.000	2.68	0.362*		
Explained variability			13.1% (8.9% after cross-validation)				
Relevant predictors (matrix X)	IL-2	-0.465	-18.42		-0.058	-2.93 *	
	IL-4	-0.483	-18.85		-0.063	-2.54 *	
	IL-7	-0.441	-9.92		-0.048	-2.50 *	
	MCP-1	-0.473	-7.53	-0.188 **	-0.082	-2.50 *	
	RANTES	-0.406	-8.57	-0.142 **	-0.045	-1.99 *	
	(matrix Y)	Animal-reminder disgust	1.000	1.23	2.442		
Explained variability		6.2% (4.3% after cross-validation)					

R - component loadings expressed as correlation coefficients with predictive component. *P < 0.05. **P < 0.01.

Table 4

Relationships between NVP (Rhodes Index) and predictors as evaluated by OPLS model and multiple regression (for details see Statistical analysis).

	Variable	OPLS, Predictive component			Multiple regression		
		Component loading	t-statistics	R	Regression coefficient	t-statistics	
Relevant predictors (matrix X)	Method of conception	0.121	1.55	0.278	0.022	2.77*	
	Maternal age	-0.165	-2.63	-0.393*	-0.054	-3.17**	
	IL-1β	-0.347	-9.69	-0.825**	-0.040	-4.40**	
	IL-2	-0.333	-12.40	-0.792**	-0.030	-2.27*	
	IL-4	-0.373	-14.35	-0.885**	-0.034	-3.50**	
	IL-9	-0.205	-4.82	-0.486**	-0.050	2.17*	
	IL-17A	-0.351	-19.16	-0.834**	-0.041	-3.99**	
	Eotaxin	-0.332	-10.45	-0.789**	-0.037	-2.95*	
	G-CSF	-0.323	-11.92	-0.767**	-0.028	-2.98*	
	MCP-1	-0.337	-10.53	-0.801**	-0.037	-4.50**	
	PDGF-BB	-0.245	-8.64	-0.581**	-0.036	-1.69	
	RANTES	-0.289	-7.98	-0.687**	-0.052	-2.59*	
	TNF-α	-0.309	-6.44	-0.735**	-0.040	-4.95**	
	(matrix Y)	Rhodes Index	1.000	3.98	0.339**		
	Explained variability		11.5% (9% after cross-validation)				

R - component loadings expressed as a correlation coefficients with predictive component. *P < 0.05. **P < 0.01.

2020), there is evidence that early pregnancy also involves a complex activation of immune functions, including increased levels of both pro-inflammatory and anti-inflammatory cytokines (Curry et al., 2008; Jarmund et al., 2021; Mor et al., 2011; PrabhuDas et al., 2015; Spence et al., 2021). Without a sufficient immune activity in early pregnancy that is manifested in higher levels of various groups of cytokines, both the mother and the fetus become more vulnerable to pathogens which poses a higher risk of adverse pregnancy outcomes (Hedman et al., 2020;

Robinson & Klein, 2012; Yockey & Iwasaki, 2018). Indicating that disgust sensitivity is rising as cytokine levels are decreasing, our results suggest that disgust may prevent adverse consequences of insufficient immune adaptation in pregnancy by facilitating avoidance of pathogens. This appears to be effective as greater pathogen disgust sensitivity has been found to be associated with lower levels of pathogen infection (Cepon-Robins et al., 2021).

4.2. Disgust in pregnancy and immune markers

We found that higher disgust sensitivity was associated with lower circulating serum levels of various cytokines, including FGF basic, Eotaxin, IFN- γ , IL-1 β , IL-2, IL-4, IL-7, IL-17A, MCP-1, PDGF-BB, RANTES, and TNF- α . These cytokines belong in different cytokine families, including pro-inflammatory mediators of innate immunity (IL-1 β , TNF- α), Th17 (IL-17A), Th1 (IFN- γ , IL-2) and Th2 (IL-4) cytokines, hematopoietic (IL-7) and growth (PDGF-BB, FGF basic) factors and chemotactic (Eotaxin, MCP-1, RANTES) proteins. Apart from their function in immune surveillance, they exert a wide range of actions in pregnancy. IL-2 and TNF- α participate in immune surveillance and prevent excessive trophoblast invasion. IFN- γ has an essential role in early placentation and trophoblast invasion regulating vascular remodeling. IL-4 was detected to support maternal-fetal tolerance, IL-17 promotes trophoblast invasion, chemokines (RANTES, Eotaxin, and MCP-1) drive circulating leukocytes to decidua and are involved in endometrial communication with the trophoblast (Wang, Sung, Gilman-Sachs, & Kwak-Kim, 2020). PDGF-BB signalling is involved in early fetal hematopoiesis (Andrae, Gallini, & Betsholtz, 2008). IL-1 β participates in the regulation of implantation and placental development; undetectable serum level of IL-1 β was associated with subsequent pregnancy loss after IVF (Kreines et al., 2018). The exact role of IL-7 in pregnancy has not yet been clarified, however, as a hematopoietic factor, it promotes the development of $\gamma\delta$ T cells and decidual NK cells, providing a tolerogenic environment (ElKassar & Gress, 2010; Tagoma et al., 2019). Importantly, it must be noted that the circulating serum cytokine levels and the local cytokine levels (in the placenta and uterus) may differ. For example, it was documented that the proportion and levels of detected cytokines varied in both serum and cervicovaginal fluid across all three trimesters of pregnancy (Ashford et al., 2018). An altered profile of local cytokines may represent pathologies at maternal-fetal interface associated with impaired fetal growth and development (Yang, Zheng, & Jin, 2019), while serum cytokine levels are associated with both pregnancy and immune status (Stokkeland et al., 2019).

Although the overall cytokine profile we found to be significantly associated with disgust sensitivity is rather pro-inflammatory, to interpret our results in terms of the individual cytokine functions is challenging as one cytokine may be responsible for various effects, but at the same time, different cytokines may serve the same function or exert synergistic or additive effects. Nevertheless, it is important to point out that the individual cytokines are part of a more extensive regulatory network responsible for the integrated immune activity, while the exact role of the individual cytokines in the complex immune network of pregnancy is yet to be determined. As we found associations between disgust sensitivity and various cytokines in the same direction (i.e., higher disgust was related to lower serum cytokine concentrations), we interpret higher disgust sensitivity as indicative of an insufficient adaptation of this complex immune system as a whole.

4.3. Disgust subscales and immune functioning

Our finding that the Contamination and Core (but not Animal-reminder) disgust are significantly associated with the immune system functioning in early pregnancy is in line with the CPH as these subscales refer to the transmission of pathogens (interpersonal transmission and transmission through infected food, animal or bodily products). In fact, should disgust sensitivity provide a protection against pathogens to those pregnant women who do not develop sufficient immune activation, both Contamination (interpersonal transmission of essences) and Core (bodily products such as urine, vomit, and mucus; animals associated with garbage such as rats or cockroaches; or rotten food such as expired milk) disgust would indeed be the effective defense. Additionally, it is in accordance with our hypothesis that we found no association between Animal-reminder disgust and immune activity, as this domain refers to situations and substances that remind us of our mortality and

risks of bodily injuries, not of potential sources of pathogens.

4.4. Disgust sensitivity and white blood cells count (WBC)

We found no association between disgust sensitivity and white blood cells (WBC) count, which is considered an immune marker and correlates with cytokine levels and the organism immune status under both physiological and pathological conditions. This result is not in line with our hypothesis, as we expected immune markers to be negatively correlated with disgust sensitivity. On the other hand, the decrease in WBC count signalizes more severe pathologies, while our sample consisted of generally healthy women. Another explanation for this result could be that we only assessed the total WBC count in our study as we did not have data regarding the leukocyte subpopulations (e.g. granulocytes and lymphocytes). However, the WBC subsets are changing more than the total WBC in pregnancy, and data related to the WBC subsets could therefore provide a more detailed picture than the WBC count alone (Abu-Raya, Michalski, Sadarangani, & Lavoie, 2020; Bert, Ward, & Nadkarni, 2021).

4.5. Nausea/vomiting in pregnancy and cytokine levels

We observed negative associations between NVP and various cytokine levels (the individual cytokines functioning as significant predictors were similar in the model for NVP and disgust sensitivity), suggesting that nausea and vomiting may too have a protective function in early pregnancy, which is in line with previous studies linking nausea in pregnancy with a lower risk of miscarriage, preterm birth and congenital heart defects (Boneva, Moore, Botto, Wong, & David Erickson, 1999; Czeizel & Puhó, 2004; Hinkle et al., 2016). Interestingly, the association between cytokines and disgust sensitivity was considerably more robust than that between cytokines and NVP, suggesting that disgust plays a decisive role in the behavioral immune system activated in early pregnancy.

4.6. Disgust and the length of pregnancy

Evaluating the effects of covariates, we observed that women in the later phase of the 1st trimester of pregnancy reported a significantly higher overall DS-R score and the Core disgust score compared to those in earlier phase of the 1st trimester. Thus, disgust sensitivity appears to be increasing with advancing pregnancy in the 1st trimester, especially disgust sensitivity related to items such as spoiled food or bodily products (Olatunji, Haidt, McKay, & David, 2008), suggesting that disgust sensitivity growing in early pregnancy is strongly related to food rejection rather than to avoiding other potential sources of pathogens, such as interpersonal contacts.

4.7. Disgust and the method of conception

In the model assessing the association between Contamination disgust and cytokine levels, the method of conception was significantly associated with Contamination disgust scores, suggesting that previous fertility treatment increases disgust sensitivity in pregnancy. This is in line with our expectations as women undergoing fertility treatment often use synthetic corticosteroids such as prednisolone that have a suppressing effect on the immune response.

4.8. Strengths and limitations

This study's main contribution is that we showed, for the first time, the association between disgust sensitivity and immune system activity indices (serum cytokine levels) in pregnant women's blood serum. Moreover, our study is based on a relatively large sample size. Several limitations must however be acknowledged. Most importantly, although cytokine levels served as the variable predicting disgust sensitivity in

our analyses, the mean length of pregnancy when the DS-R was completed by the pregnant women was slightly shorter than that when blood samples for cytokine analyses were collected. However, there was an overlap of the intervals when both data types were collected (DS-R was completed between the 4th and 12th week, while blood samples between the 9th and 14th week). On a conceptual level, it must be acknowledged that although we presumed that disgust sensitivity is predicted by immunity markers as our aim was to test the CPH, the opposite direction of causality is a reasonable explanation as well. In fact, increased cytokine levels may indicate not only immune preparedness but also the immune response to the pathogen exposure (Petroni et al., 2021). Therefore, the association between higher disgust and lower cytokine levels may also be interpreted in the way that higher disgust prevents from the pathogen exposure, i.e. that higher disgust sensitivity predicts lower cytokine levels and not the other way around. Indeed, Stevenson, Case, and Oaten (2009) showed that higher disgust sensitivity was associated with fewer illnesses.

Another limitation is a relatively low internal consistency of the DS-R subscales Core and Contamination disgust, but the internal consistency of the DS-R as a whole was satisfactory. In future studies, the use of other scales such as the Three Domains of Disgust Scale (TDDS) (Tybur, Lieberman, & Griskevicius, 2009) that contains a highly reliable subscale Pathogen disgust (Olatunji et al., 2012) is encouraged. Lastly, our hypothesis is based on a recent view characterizing early pregnancy as a state of complex immune activation (Hedman et al., 2020; Peterson et al., 2020), but we only had data from pregnant women and not from the pre-pregnancy period at our disposal, so we were not able to compare disgust or immune indices levels before and during pregnancy. Although extremely demanding, such a longitudinal approach could deliver even more compelling evidence for the CPH than assessing the associations between disgust sensitivity and indices of immune activation in early pregnancy.

5. Conclusion

Indicating that higher disgust sensitivity could be regarded as an early warning sign of insufficient immune adaptation in pregnancy, our results have relevant clinical and public health implications. Given the detrimental consequences of immunity-related disorders in pregnancy for both the mother and child, a screening for disgust sensitivity in early pregnancy could enable timely detection and intervention. Further research is needed to reinforce our findings and, if compelling evidence for the association between higher disgust sensitivity and suboptimal immune system activity arises in the future, a cutoff score on a disgust measurement scale indicating a risk of potential immune dysfunction should be determined to be used in clinical settings.

Data availability

The raw data are available at <https://doi.org/10.6084/m9.figshare.14500374.v2>.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.evolhumbehav.2022.02.001>.

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