

## Comment on the Recent Publication in “The New England Journal of Medicine” : “Trends in Mental Health Care among Children and Adolescents” (Olfson et al., 2015)

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### Introduction

The recently published by Olfson et al. in “The New England journal of Medicine” manuscript describes increased proportion of youths receiving outpatient mental health service for mental health problems in children and adolescent with less severe or no impairment in the United States [1]. This manuscript is one of the many reports published in the past couple of years, which describe the alarming trends in the mental health of future generation [2-4]. The causes, underlying these conditions, are numerous and involve complex interaction between genetic and epigenetic factors [5], the latter includes social environment, nutrition, environmental pollutants, etc. [6-8]. Interestingly, authors found that “the odds of more severe mental health impairment were greater among adolescents than among children, among male youths than among female youths, and among non-Hispanic white youths than among Hispanic youths”. This finding points out that the insults in the different time-periods of brain development might play the different role in the mental health disorders. The in-utero brain development is particularly susceptible to the environmental challenges: phenomenon, termed developmental origin of adult diseases [9-11]. The increased susceptibility of the male fetuses to the adverse intrauterine conditions is well documented in animal models and human studies [12,13]. This editorial review focuses on the prenatal and early postnatal origin of the mental health problems, describing the role of maternal environment and paternal involvement in the offspring’ mental health.

### Maternal Effect

#### Maternal obesity and the mental health of the offspring

Maternal obesity, affecting 20.2-34% of all pregnant women remains a major factor influencing the development of offspring health in later life as shown by the experimental animal models and observed in longitudinal clinical studies in humans [14-17] (Table 1).

The mechanisms behind the adverse effect of maternal obesity are under intensive investigations; however the plausible explanations are non-existent. One of the possible mechanisms is obesity-associated inflammation. Chronic inflammation is the fundamental characteristic of obesity [35-38]. In pregnancy the inflammatory state extends to the fetus through placenta [39-42]. Placental inflammation in maternal obesity has been described in humans [42-44], rodents [45,46], ruminants [47] and non-human primates [48], including our own publication in baboons (*Papio spp.*) [49]. These placental inflammatory changes are altering placental and fetal brain functions, since placenta does not simply pass the nutrient and endocrine signals to the fetus, but actively modulates fetal brain development [50,51], [52-54]. The brain is the central target organ of the obesity-related inflammation in adults [37,55,56]. In fetuses the inflammatory brain responses to maternal obesity have been documented in animal models: non-human primates [57] and rodents [58,59], moreover, the activation of inflammatory pathway was recently reported in human fetal brain [60]. Inflammatory pathways are crucial in perinatal brain injuries and are

Fetal outcome and developmental consequences of MO	Level of evidence in human population	References
Stillbirths	Systematic review and meta-analyses of population-based studies. Cross-sectional study, cohort study, CEMACH report (UK).	[18-25]
Increased infant mortality	Meta-analyses	[26]
Intrauterine growth restriction	Cohort study	[27]
Large for gestational age, high birth weight, macrosomia	Systematic review and meta-analyses	[28]
Neurological and behavioral disorders in the offspring (Autism, ADHD, eating disorders, schizophrenia).	Cohort studies, systematic review, meta-analyses	[29-31]
Preterm birth	Cohort studies	[32,33]
Premature mortality in adult offspring	Follow-up of 1 323 275 person years.	[34]

**Table 1:** Maternal obesity (MO), pregnancy outcome and offspring health in human population.

targets of perinatal brain protection [61-64]. Thus, targeting maternal obesity therapies might save the mental health of children and adults and decrease annual service use among youths with less severe or no impairment.

#### The exposure to the sun-light and programming of the offspring behavior

Solar radiation, which includes the visible and ultraviolet spectrum, is the most important environmental factor, essential for sustaining life, the degrees of UV light exposures have been related to incidences of different pathologies, including ageing, cancer and neurological disorders [65,66]. It has been shown, that the absence of solar radiation

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has direct correlation with aggressive human behavior and the incidences of wars [62]; the seasonality of mental disorders, including aggression is well documented [67]. Solar light in general seems to be the fundamental regulator of aggression [68]. The complex behavioral patterns, associated with the aggression and seasonality are linked to the testosterone level [69]. Indeed, the experimental studies in animal models and population studies in humans demonstrated that maternal hyperandrogenism is associated with behavioral abnormalities in offspring [70-72].

### **Maternal stress as a key factor in programming of the offspring' mental health**

Maternal stress is a well-documented risk factor for the mental and behavioral problems in offspring through the mechanism of increased fetal exposure to glucocorticoids [11,73,74]. The synthetic glucocorticoids are commonly used in the treatment and prevention of preterm labor [75], creating the artificial stress-environment for the fetus. However the benefits of prenatal glucocorticoid administration for the preparation of premature babies to the life outside of the womb include significantly reduced newborn morbidity and mortality [76], there is evidence from the systematic meta-analyses, demonstrating altered behavioral reactions to stress and perceived stressors in children [75]. The experimental studies in non-human primates showed, that three courses of betamethasone administration [77] during pregnancy negatively affect the motivational and learning behavior in the offspring [78]. The mechanism of these adverse effect involves glucocorticoid receptor pathways that impact action in neural stem/progenitor cells proliferation [79]. The consequences of prenatal glucocorticoid administration depend on the type of glucocorticoids used (e.g. dexamethasone is not inactivated by placental 11 $\beta$ -HSD type 2 enzyme, while hydrocortisone does), stage of the brain development and maternal care after birth [80]. Importantly, maternal care after birth could alleviate effect of the prenatal dexamethasone exposure.

### **Maternal nutrition and offspring mental health**

Maternal nutrition, including dietary pattern [81], over-[31,82] and undernutrition [83] and selective nutrients intake [84], is associated with the offspring mental and behavioral status in later life. The mechanisms, explaining dietary effects comprise among others glucocorticoid excess [85], inflammation [82], impaired metabolic processes [86]. Prenatal undernutrition alters developmental brain trajectories [87], with the subtle changes, that might have profound effect on the offspring mental health [88,89]. Importantly, the prenatal nutrient intervention could have both positive and negative effects. The prenatal choline supplementation, for example, rescued the male offspring, exposed to maternal stress from the development of the adult anxiety-related behaviors [90].

### **Paternal Effect**

Paternal involvement in pregnancy outcome is demonstrated through the several lines of evidence. The parental separation in the prenatal period, for example, has a profound effect on the offspring metabolic health [91]. Father's involvement has received limited attention in psychological research [92]. A father's relationship with his children is distinct from mother – child relations [93]. Relationship with father is encouraging his children to be competitive and independent. The fathers may be particularly influential in the development of certain aspects of child behavior. The presence of a father in the family also has indirect influences, including that of father's continued financial support of his children can affect children's outcome by influencing

the economic structure of the household. The marital problems disrupt fathering more than mothering; therefore the positive child's outcomes are associated with paternal involvement. This may be attributed to harmonious co – parenting relations. There is evidence that only father – child relationships are significantly related to sense the stress [94]. More recently, it has been shown that closeness with his fathers during childhood was positively related to adult daughters and sons educational and occupational mobility, psychological adjustment and psychological well-being. Children with involved fathers tend to be more psychologically well-adjusted, do better at school, less engage in antisocial behavior and have more successful intimate relationships. Father's involvement and nurturance are positively associated with children's intellectual development, social competence, internal locus of control and the ability to empathize [95]. There is a strong association between postnatal paternal mental health status and later development of psychopathology in children [96]. The psychiatric disorders such as oppositional defined disorder, conduct disorders and paternal depression early in the children's lives are associated with persisting and clinically relevant level of disturbances. Paternal depression is specifically related to behavioral and peer relationship difficulties, which in contrast to maternal depression appears is associated with broader spectrum of child disturbance. There is a link between paternal depression and antisocial behavior in children. Depression, with core symptoms of low mood, lack of energy and loss of interest is likely to severely disrupt the ability of any parent to undertake the task of parenting, particularly affecting day-to-day interactions of parent and child. Paternal depression early in the child's life is associated with these persisting problems even when controlling for later paternal depression. The concordance of depression in partners and the consequences of depression in one partner for the other are important factors for family functioning and the developing child. Hence, depression may have an impact not only on the men themselves but also the development of the children. In a similar study, it was found that depression in fathers during the postnatal period was associated with adverse emotional and behavioral outcomes in children aged 3.5 years and an increased risk of conduct problems in boys. These effects remained even after controlling for maternal postnatal depression and later paternal depression [96]. In an extension of the study by the same authors, while exploring potential environmental casual pathways and moderating effects that may explain the association between paternal depression during postnatal period and psychological problems in children age 3.5 and seven years, the findings indicated that family factors, including maternal depression, couple conflict and to a lesser extent paternal noninvolvement explain two thirds of the total effect of paternal depression on child outcomes at 2.5 years with maternal depression and couple conflict accounted for the majority of the mediation scene. Similar findings were seen in children at age 7. Paternal depression during the postnatal time appears to exert its influence on children's behavior mainly to family environment mechanisms. Mothers usually turn to their partners for emotional support after the birth of the infant and fathers with depression may have difficulty in providing family support to mothers for the care of the children [97]. On the other hand, fathers with depression during the postnatal time have reported high levels of parenting distress and the lower sense of parenting efficacy the psychosocial factors have been shown to predispose mothers to depression [98]. In summary, paternal depression during postnatal period has profound effect on children's mental health.

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