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Research Article

Prenatal Malnutrition and Its Devastating Consequences on Mental Health Later in Life

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Abstract

Objective: To investigate the effect of maternal famine and severe food insecurity on offspring. From previous studies we deduced the hypothesis that exposure to prenatal famine predisposes to addictive behaviors later in life and significantly alters sex ratios at birth. With this study we test this hypothesis.

Methods: In a case-control study we investigated the "Dutch hunger winter" period from October 1944 to May 1945. 42.292 individuals of native Dutch people were born between 1944 and 1947, 2166 individuals of them were registered with addictive behaviors. The unexposed individuals are born exactly one year after the hunger period. Exposed/unexposed ratios with and without addictive behaviors were analyzed and sex ratios were calculated. All data were quantified as Odds Ratios (ORs).

Results: Male individuals exposed to famine during their first trimester of gestation had a significantly higher risk of developing addictive behaviors than unexposed males. In female individuals significant results emerged in the third trimester of gestation. There was a significant excess of males at birth in all individuals with addictive behaviors, both exposed and unexposed to famine.

Conclusion: Addictive behavior later in life was strongly associated with prenatal malnutrition exposure in first gestational trimester in men and third gestational trimester in women. The excess of male births in all addictive behavior groups further point to a significant gender effect. A comparable excess of males is commonly known in individuals with antisocial personality traits (disorders) which in turn are regularly combined with addictive behaviors. We propose the new hypothesis that this gender effect is survival adaptive and short-termed "functional" under severe famine circumstances.

Keywords: Prenatal famine exposure; Addictive behaviors; Sex ratio at birth; Antisocial personality traits

Introduction

The global nutrition report 2017 revealed that 88% of 193 countries, 6 regions and 22 sub-regions for which data were available face some form of severe malnutrition including childhood stunting, anemia in women of reproductive age and overweight in adult women. 815 million people are going to bed hungry and 38 million people are facing severe food insecurity in Nigeria, Somalia, South Sudan and Yemen, not yet having included the number of people suffering from severe starvation in Syria and other war regions. Hunger regions in our world are mostly man made and consequences of wars, armed conflicts with civilian casualties including corrupt governments which cause lack of infrastructure for agriculture and economic development. Natural catastrophes like severe droughts, often also complicated with armed conflicts, which can dramatically worsen water and food shortage [1]. The short and long-term consequences on individuals which are prenatally and early postnatal exposed to severe famine are still not well known in humans.

The Dutch "hunger winter" is one of most studied extreme hunger periods because of its sharply defined period. In World War II the German authority commanded a total embargo on occupied Netherlands in October 1944 for assisting the Allied troops in the well-known operation "Market Garden". Consequently, food rations declined substantially between February and May 1945, resulting in an individuals' calorie intake far below 800 kcal per day. Approximately 22,000 persons out of the 3.5 million inhabitants of the western part of the Netherlands eventually died during mid-October 1944 to mid-May 1945 as a result of the hunger exposure [2]. After the liberation the food depletion rapidly subsided and by June 1945 the individuals' average calorie ingestion had again risen to more than 2000 kcal per day [3]. The exposure to the prenatal nutritional depletion was found to be associated with Spina bifida and anencephaly and an increased susceptibility of multiple chronic somatic and mental problems in later life and even trickles-down to the second-generation offspring. These problems include obesity, coronary heart disease and other cardiovascular problems, glucose intolerance, disturbed blood coagulation, cancer and mental diseases such as schizophrenia, schizophrenia spectrum disorders, affective disorders and antisocial personality disorders [4,5]. In addition, a recent study on the "Dutch hunger winter", restricted to the Rotterdam area, found a strong association between prenatal exposure to maternal nutritional deficiency during the first trimester of gestation and male offspring with addictive behaviors in the adult, however not in the female offspring [6].

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Another finding of this study was that individuals with addictive behaviors in both samples exposed and unexposed prenatally to the hunger period, 2 to 3 times as many boys than girls were born, while apparently the gender ratio of males to females at time of birth in the absence of manipulation is remarkable constant with only small alterations in a population around the globe and during the last centuries of about 105 boys to 100 girls (=1.05) [7-11].

The objective of the present study is to test the hypothesis that in an extended population, exposed to a sharply defined severe hunger period, maternal (prenatal) exposure to famine can cause addictive behaviors later in life in the offspring and substantially alters the birth ratio male to female.

Methods

Study population

The study is conducted by means of an extended case-control design in which populations of the six main cities in the Western part of the Netherlands, that were all struck by the famine during the "Dutch hunger winter" 1944-1945, were included. The study population included 42.292 native Dutch inhabitants. These individuals were born in the period of 1944-1947 and were living in the six main cities that were occupied during the hunger winter in the Western part of the Netherlands: Amsterdam, Haarlem, Leiden, Den Haag, Utrecht and Rotterdam. 2,166 individuals from them were also registered with any (illicit) substance use disorders obtained from the databases of the local Dutch mental health care institutes of the listed cities. Information of both the samples with and without addictive behaviors later in life was obtained in August 2009.

Definition of exposure

The hunger period started from 15th October 1944 to 12th May 1945 [3]. Between 1st February until 12th May 1945 the famine was the most severe and the average daily food intake went down far below 800 kcal (4200 kJ), which is considered a biologically validated cut-off point for prenatal mortality, and therefore was defined as the "peak of the hunger period". The estimated average daily caloric content of the food contained 14 g to 22 g of proteins, 114 g to 144 g carbohydrates, and 12 g to 28 g of fat [12].

The daily food consumption consisted of an increasingly meager nutrition of bread, potatoes, tulip bulbs and sugar beets. This nutritional depletion does not only capitalize on calorie and protein intake, but also on the lack of key micronutrients, including folate, essential fatty acids, vitamin A, D, other retinoids, and iron [13]. The gestational famine effect was divided in three trimesters, of 94 days [6]. For each individual, the date of conception was calculated, by subtracting 282 days from the date of birth. Individuals who were conceived in the hunger period were considered to be exposed at least for one of these trimesters in a time-window of minimal two weeks in that trimester. Individuals were defined as unexposed when they were conceived during the equivalent period in the subsequent year. Subgroups of the subjects were exposed during two trimesters. Consequently, for exposure to the peak of the hunger period, the sample was stratified in five groups: exposure only to the first, to the second or to the third trimester, and overlapping exposure to the first and second trimester and to the second and third trimester (Figure 1).

Data analysis

Generally, in case-control studies the Odds Ratio (OR) is considered eligible where events are typically exceptional [14]. For each trimester in the exposed and unexposed samples we calculated the proportion of individuals with and without addictive behaviors and sex ratios male to female by means of ORs, followed by 95% Confidence Intervals (CI). Pearson's chi square tests were employed to test differences between the proportion of exposed and unexposed males and females in individuals with and without addictive behaviors later in life. All p-values were 2-sided and considered significant at $p<0.05$.

Results

Table 1 presents the number of exposed and unexposed individuals with and without addictive behaviors during five pre-stratified periods of gestation in the peak of the hunger period. The odds of exposure among male individuals with addictive behaviors was significantly higher than the odds of exposure among male individuals without addictive behaviors in the first trimester (OR=2.71), but not in female individuals. However, in the third trimester the odds of exposure was significantly higher among female individuals with addictive behaviors (OR=1.89), but not in male individuals. None of the other comparisons yielded a statistically significant difference.

Table 2 provides the figures pertaining to the number of males/females in individuals with and without addictive behaviors who were exposed and unexposed to the peak of the hunger period, with minimal overlap between birth cohorts. All calculated ORs were statistically significant. The ORs of sex differences among the exposed individuals with addictive behaviors range from 1.68 (only 3rd trimester) to 4.92 (only 1st trimester). The ORs regarding sex differences among individuals with addictive behaviors of the unexposed groups range between 1.50 (1st and 2nd trimester) and 3.12 (only 1st trimester).

Discussion

In animal studies it is well known that nutrition is probably the single greatest environmental influence both on the fetus and neonate, and plays a necessary role in the maturation and functional development of the central nervous system. Malnutrition has been found to adversely affect the developing brain not only during the brain growth spurt period, but also during early organizational processes such as neurogenesis, cell migration and final cell differentiation [15,16]. In malnutrition insult it comes to global, not focal, brain pathology and developmental failures that adversely alter the organism's ability to interact and cope with its environment [17-19]. Very important for a society have been judged the cases of suboptimal brain development, generally referring to the non fulfillment of the entire genetic potential of the individual if there is lack of proper food, poor and/or inadequate diet or starvation. There is evidence that malnutrition occurring only during pregnancy is less harmful than malnutrition begun one month prior to mating and continued throughout pregnancy and that the fetal brain is most vulnerable when there is severe combined pre-pregnancy and gestational (maternal) malnutrition [17-20]. Recently it has been shown that the short pre-implantation period of the embryo is very critical for the embryo's interaction with external, maternal factors, particularly the nutritional status. It is suggested that these interaction mechanisms straddle epigenetic, molecular, cellular and physiological levels of biology and that this very early (pre-implantation) development is very crucial for health outcomes in human lives [20].

Both, pre-pregnancy and severe gestational malnutrition happened during the studied hunger period and, additionally, not only mothers but also the fathers suffered from severe starvation. As a consequence we have found a firm association between

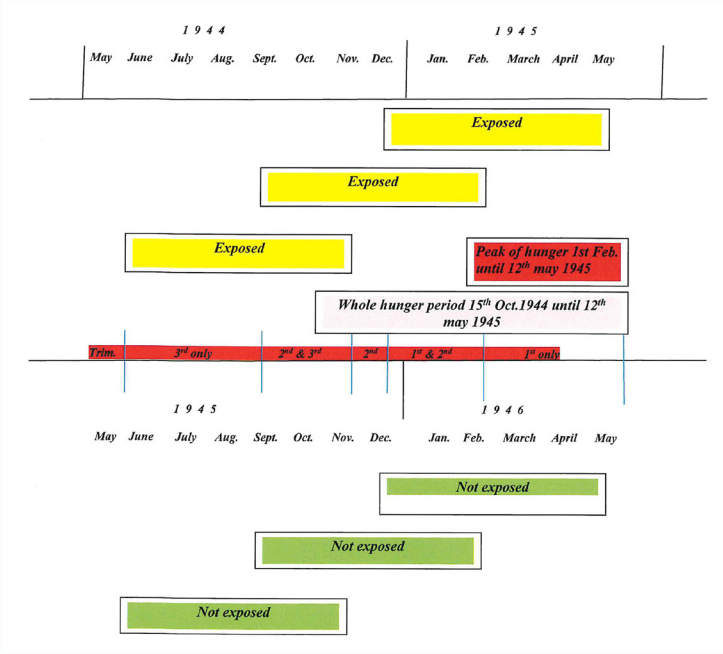

Figure 1: Definition of exposure and not exposure to the hunger winter for the first, second and third trimester of gestation with overlap during two trimesters (first and second, or second and third).

Table 1: Prenatal (un) exposure to the peak of the hunger winter (<1000 kcal/day) in individuals with and without Addictive Behaviors (AB), with minimal overlap between birth cohorts.

		Without AB	With AB	OR (95% C.I.)	P
Only 1st Trimester					
Men	Exposed	833	93	2.71 (2.01 - 3.65)	***0.000
	Unexposed	2230	92		
Women	Exposed	794	18	1,71 (0.95 - 3,10)	0.073
	Unexposed	2190	29		
1st and 2nd Trimester					
Men	Exposed	616	40	1.19 (0.92 - 1.73)	0.369
	Unexposed	1849	101		
Women	Exposed	591	21	1.31 (0.79 - 2.19)	0.3
	Unexposed	1456	53		
Only 2nd Trimester					
Men	Exposed	251	30	1.29 (0.80 - 2.06)	0.293
	Unexposed	581	54		
Women	Exposed	275	12	1.37 (0.67 - 2.83)	0.39
	Unexposed	660	21		
2nd and 3rd Trimester					
Men	Exposed	984	72	1.23 (0.91 - 1.66)	0.175
	Unexposed	2150	128		
Women	Exposed	1034	31	1.17 (0.75 - 1.82)	0.499
	Unexposed	2215	57		
Only 3rd Trimester					
Men	Exposed	1519	116	1.11 (0.87 - 1.41)	0.393
	Unexposed	2804	193		
Women	Exposed	1538	70	1.89 (1.34 - 2.67)	***0.000
	Unexposed	2713	63		

Note: OR: Odds Ratio; CI: Confidence Interval. Unexposed individuals are born in the equivalent period in the subsequent year. *p<0.05, **p<0.01, ***p<0.001

prenatal exposure to famine and addictive behaviors in later life and additionally we found a strong gender effect with respect to the pre-stratified periods. Males that sustained a severe nutritional deficiency during the first trimester of their prenatal development (OR=2.71) and females exposed in the third trimester (OR=1.89) were at risk to develop addictive behaviors later in life.

The development of addictive behaviors in later life may be caused by a critical Neuro-developmental disruption of the brain reward system [21]. Although the exact mechanism of action is unknown, malnourishment is associated with a deterioration of physiological well-being including muscle, cardiac, and immune function problems and is coupled with life-threatening diseases such as severe infection, gastrointestinal and respiratory conditions. In addition, there is also a strong relationship between chronic stress and immunological changes [20,22]. Exposure to severe hunger and extreme stress caused by life threatening situations like armed conflicts therefore may doubly impact the immune system by blending a weak immune function with an extremely stressful episode, causing childhood neglect, abuse and trauma, and impaired maternal care giving. That said, it has been suggested that alterations of the mothers' immune system and consequently such maternal immune responses may lead to a Neuro-developmental deposition of the offspring [23,24]. It appears that the timing of the nutritional deficiency plays an important role when it

Table 2: Sex ratio regarding prenatal (un) exposure to the peak of the hunger winter (<1000 kcal/day) in individuals with and without Addictive Behaviors (AB), with minimal overlap between birth cohorts.

		Without AB	With AB	OR (95% CI)	p
Only 1st Trimester					
Exposed	Male	833	93	4.92 (2.95 - 8.23)	***0.000
	Female	794	18		
Unexposed	Male	2230	92	3.12 (2.04 - 4.75)	***0.000
	Female	2190	29		
1st and 2nd Trimester					
Exposed	Male	616	40	1.83 (1.06 - 2.98)	*0.025
	Female	591	21		
Unexposed	Male	1849	101	1.50 (1.07 - 2.11)	*0.025
	Female	1456	53		
Only 2nd Trimester					
Exposed	Male	251	30	2.56 (1.28 - 5.11)	**0.005
	Female	257	12		
Unexposed	Male	581	54	2.92 (1.74 - 4.89)	***0.000
	Female	660	21		
2nd and 3rd Trimester					
Exposed	Male	984	72	2.44 (1.59 - 3.75)	***0.000
	Female	1034	31		
Unexposed	Male	2150	128	2.31 (1.68 - 3.18)	***0.000
	Female	2215	57		
Only 3rd Trimester					
Exposed	Male	1519	116	1.68 (1.24 - 2.28)	**0.002
	Female	1538	70		
Unexposed	Male	2804	193	2.96 (2.22 - 3.96)	***0.000
	Female	2713	63		

Note: OR: Odds Ratio; CI: Confidence Interval. Unexposed individuals are born in the equivalent period in the subsequent year. *p<0.05, **p<0.01, ***p<0.001

affects organ systems and thus the type of disorder [25]. For instance, affective disorders have been associated with middle to late gestational famine, albeit the relationship seems not to be gender specific [26].

The gender ORs in both the exposed and unexposed individuals with addictive behaviors of the present study ranged between 1.50 and 3.12 with a peak in the first trimester among exposed male individuals (OR=4.92). This means 1, 5-5 boys were born to 1 girl. This strongly surpasses the previously reported weak excess (OR=1.31) of male offspring during the hunger period and corroborates that addictive behaviors are roughly two to three times higher among men than women [27-29].

Consistent with previously conducted research, also other externalizing mental disorders, that are primarily occurring in the male offspring, were associated with nutritional deficiency in the early stage of pregnancy, such as Antisocial Personality Disorder (ASPD) [30]. It has been shown that the prevalence of ASPD in general is estimated to be three times higher in patients with substance use disorders, and ASPD is highly comorbid among men with substance use disorders [31-33]. Consequently, it has been suggested that substance use disorders and ASPD may share common underlying neuropsychological pathways, characterized for instance by an impaired inhibitory control and vulnerability for immediate gratification.

However, there may be an additional etiological explanation. The aforementioned impairments may be considered as (genome-epigenetic based) survival adaptive and functional under severe famine and stress circumstances, whereas the offspring should be instinct reward-seeking individuals that discount the future in favor of the immediate consequences. It seems viable that such individuals, for examples soldiers who are mostly men, may need antisocial personality characteristics in an evolutionary way to stay alive by acquiring and maintaining food and safety for their own population group by exhibiting high levels of impulsivity, lack of remorse for opponents when fighting against other population groups, disregard for their own safety. Furthermore, hunger and bad life circumstances can "exacerbate antisocial personality traits" in otherwise normal personalities as we can daily see and hear in news reports about refugee camps and war regions in our world. These characteristics may be understood as 'functional' antisocial personality traits of environmental adaptation, such that a severe prenatal exposure to famine and maternal stress may have a critical impact on the developing brain during sensitive periods. For instance, it has been substantiated in animal studies (birds) that mothers are capable to transfer adaptive information about predation risk to their offspring as a result of an environmental manipulation [23]. It has been shown that the offspring of predator–exposed mothers exhibited an acceleration of wing growth and longer wings at maturity than controls. It was concluded that rapid environmental changes such as predation risk may elicit functional maternal effects [23]. The study highlights the call to uncover the gene–environment interplay that determines how the expression of vulnerability leads to psychopathology [34].

It seems conceivable that the consequences of malnutrition and severe environmentally stress caused by armed conflicts give cause for great concern about the crisis regions in our world that may face a high prevalence of criminal and drug related problems during their future development. It is also plausible that underprivileged subpopulations of Western countries characterized by a relatively low income, low education levels and high rates of unemployment, are at risk. For instance, it has been substantiated that a low socioeconomic status is associated with poor health, unhealthy food consumption, increased levels of morbidity and various mortality outcomes, including premature mortality [1,35-39]. In addition, these individuals have a greater propensity to suffer from mental disorders, including addictive behaviors and antisocial personality disorders [40-43]. One of the risk factors may be Pre-conceptional malnutrition of fathers and mothers and malnutrition of mothers during pregnancy (prenatal for the unborn baby) that may have been overlooked up-to-now. This seems to be potentially amenable to interventions by food and nutrition professionals lying in the domain of public health.

Two methodological issues and limitations of the study need to be addressed. Firstly, the data of the study population of the six cities were obtained from the municipal statistic departments (42.292 individuals) and no information was available about their health status. The data of individuals with addictive behaviors (2166 individuals) were collected from the mental health care institutes and form a subgroup of the whole population. Thus, the results may present even an underestimation of the famine effect. Secondly, one could argue that the effects found in this study are confounded by the presence of co-morbidity with other mental disorders. However, the study predominantly demonstrates an association between addictive behaviors later in life and exposure to famine during the first trimester of gestation in men and exposure during third trimester in women. In addition, the constellation with the highly significant altered sex ratio male to female with a peak in the first trimester exposed individuals in favor of male births has never been reported before. This makes it unlikely to be a major confounder of the results.

Conclusion

Our study demonstrates that gestational exposure to famine increases the risk of addictive behaviors later in life in both men and women. The crucial sensitive periods during gestation are different for men and women. Men are most vulnerable after exposure in the first trimester, women after exposure in the third trimester. Furthermore, the gender distribution at birth between males and females is significantly affected in all individuals with addictive behaviors later in life. The predisposition of addictive behaviors in prenatally famine and stress exposed individuals seems to be strongly gender-related in favor of men, as it is also obvious in individuals with antisocial personality traits (disorders). The concluding hypothesis is open for scientific discussion and research: Pre-conceptional exposure to severe malnutrition and life threatening stress of mother and father has a critical impact on sex determination in favor of male offspring. Prenatal and early postnatal exposure to malnutrition has a critical impact on the developing brain with the consequences of predominant antisocial personality traits in the offspring that can be understood as a Darwinian selection process.

The study demonstrates dramatic long-term consequences of a relatively short-term exposure to famine and malnutrition in a human population. Other potential relationships between addictive behaviors, antisocial behaviors, and sex ratio such as the influence of an unbalanced diet, exposure to infectious diseases, exposure to severe environmental pollution, and exposure to severe psychological stressors and armed conflicts need to be investigated. The implications of these findings merit attention and further research for the many low and middle-income countries where militancy and aggression are being employed by youths as weapons of political agitation.

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