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Is the Fetal Origins Hypothesis of Diabetes Supported by Animal Research? A Systematic Review and Meta-Analysis of the Evidence

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Abstract

The fetal programming hypothesis states that fetal undernutrition during pregnancy results in permanent changes in the offspring's metabolism. A large number of animal studies have evaluated the effect of prenatal undernutrition on later glucose metabolism.

Aim: We systematically reviewed the existing animal literature examining effects of prenatal undernutrition on glucose and insulin metabolism.

Methods: An electronic search was performed in Medline and Embase to identify all articles that reported studies investigating the effect of prenatal undernutrition on plasma insulin, plasma glucose and beta cell mass in animal models. Summary estimates of the effect of prenatal undernutrition on mean glucose concentration, insulin level, and beta cell mass were obtained through meta-analysis.

Results: The search resulted in 1827 articles, of which 117 were potentially eligible, based on title and abstract, and 49 met the selection criteria and were included in the review. Prenatal protein restriction (but not general undernutrition) increased plasma glucose concentrations (0.42 mmol/l (95% CI 0.07 to 0.77)). Both prenatal general undernutrition and protein restriction reduced plasma insulin concentrations (general undernutrition: -0.03 nmol/l (95% CI -0.04 to -0.01), protein restricted: -0.04 nmol/l (95% CI -0.08 to 0.00)) and beta cell mass (general undernutrition: -1.24 mg (95% CI -1.88 to -0.60), protein restriction: -0.99 mg (95% CI -1.67 to -0.31)). In all cases, heterogeneity was significant.

Conclusions: Despite significant heterogeneity, evidence from experiments in different species suggests that prenatal undernutrition – both general or protein restriction – results in increased glucose and reduced insulin concentrations as well as beta cell mass in later life.

Keywords: Prenatal undernutrition; Fetal programming; Animal studies; Glucose metabolism; Insulin metabolism

Introduction

In the early 1990s, a cohort study of 64-year-old men in Hertfordshire revealed an inverse association between birth weight and glucose concentrations and insulin resistance [1]. Subjects with the lowest birth weights were 6 times more likely to develop type 2 diabetes or impaired glucose tolerance than those with highest birth weights. These findings led to the 'fetal origins hypothesis', stating that fetal adaptations to reduced nutrient supply predispose to impaired glucose tolerance and type 2 diabetes in adult life [2]. Since, many studies in various populations across the world have investigated the association between birth weight and later risk of type 2 diabetes [3]. A systematic review of human studies on birth weight and type 2 diabetes demonstrated that in most of the middle-aged populations, there was an inverse, graded and independent association between birth weight and risk of type 2 diabetes [3]. Although the inverse association was shown to be the dominant one in most populations, various studies also find a positive association between birth weight and type 2 diabetes risk at the higher end of the birth weight distribution (> 4 kg). This would be biologically plausible given the recognized association between gestational diabetes and macrosomia.

Birth weight, however, is only a proxy for maternal undernutrition during gestation and the epidemiological studies in humans are observational, hampering the ability to draw definite conclusions on causality. Animal models allow us to experimentally study the effects of maternal undernutrition during gestation on glucose and insulin metabolism. There is a wealth of animal models used to investigate the developmental origins of type 2 diabetes. Therefore we systematically reviewed the literature on prenatal undernutrition and glucose and insulin metabolism in animal studies and used meta-analysis to obtain summary estimates of the effects of prenatal undernutrition on plasma glucose, insulin and beta cell mass.

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Methods

Search strategy

We performed a search in the electronic databases Medline (1951-January 2011) and Embase (1980-January 2011) to identify all articles that reported on fetal undernutrition and plasma insulin, plasma glucose and beta cell mass as diabetes-related outcomes in experimental animal studies. The search terms (MESH and free text) 'undernourished', '(fetal) malnutrition', 'famine', 'starvation', 'caloric restriction', 'protein restriction', 'low protein diet', 'low calorie diet', 'pregnancy', 'diabetes', 'glucose metabolism', 'glucose', 'insulin metabolism', 'insulin' and 'beta cell mass' were used. Only articles written in English were included. After screening of titles and abstracts, two reviewers independently examined full text articles and extracted data on study characteristics, quality and results. Reference lists of reviews and relevant papers were hand searched for additional relevant papers.

Study selection

We included studies that provided data describing outcomes in experimental animal models of prenatal undernutrition that reported on plasma glucose, plasma insulin or beta cell mass as measures of outcome. Prenatal undernutrition included low protein malnutrition and general caloric malnutrition. Studies had to report outcomes in comparison to control animals that were born to a mother that was normally fed throughout pregnancy. Eligibility was evaluated independently by two readers. Disagreements were resolved in consensus discussions.

Data extraction

Two reviewers independently extracted information on study design, exposure period, animal species and type of undernutrition. To assess methodological quality, data on allocation concealment, randomization, blinding and sample size calculation were extracted. When more than two experimental groups were formed, we focused on the experimental group with malnutrition in pregnancy alone. When outcome in offspring was measured at multiple time points, we chose the oldest age at which the measurements were taken. When multiple groups were measured at different ages, both age groups were included. If results were only displayed graphically, outcome was read as precise as possible. Studies that reported results as mean and standard deviation or standard error, and number of animals per group were used for meta-analysis. Data on plasma glucose, plasma insulin and beta cell mass were converted to mmol/l, nmol/l and mg, respectively.

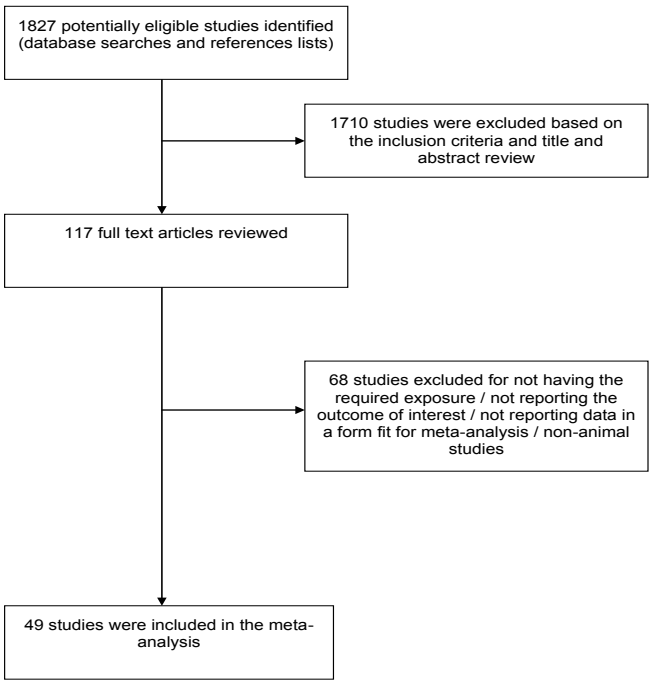

Figure 1: Literature search results for publications reporting on prenatal undernutrition with regard to glucose and insulin metabolism.

Statistical analysis

Data were analyzed using Review Manager Version 5.0. To examine potential publication bias we constructed funnel plots. We examined the possible heterogeneity in results across studies by calculating the I^2 statistic.

Summary estimates of the effects of prenatal undernutrition were obtained using a random effects model for meta-analysis, which accounts for both within- and between- study variability. Separate estimates were obtained for model type (protein or general malnutrition) and outcome measure (plasma glucose, plasma insulin and beta cell mass). The summary effects were expressed as mean difference with 95% confidence intervals (CI). When significant statistical heterogeneity was detected, the sources of heterogeneity were explored and subgroup analyses were performed for different species, sex, experimental regimens or ages at examination. To evaluate the robustness of our results against influential studies, a leaving-one-out sensitivity analysis was performed (in which the analyses were repeated several times, each time leaving one of the studies out to examine that individual studies' influence on the overall outcome).

Results

The search resulted in 1827 articles, of which 117 were considered potentially eligible after screening titles and abstracts (MV and ST). After reading full text articles (MV and either DY, RP or ST), 49 primary studies met the inclusion criteria and were suitable for data extraction (Figure 1). Twenty-six studies reported on protein restriction, one using a mouse model [4], and twenty-five using a rat model [5-29]. Twenty-four reported on general (caloric) undernutrition, one study using guinea pigs [30] and two on a mouse model [31,32], five using a sheep model [33-37] and 16 studies on rats [7,8,13,38-51] .

Methodological aspects

Only one study reported blinding of the investigator [34]. Randomization was reported in twenty-four studies, either randomization to the dietary regimen or randomly selecting the pups that were studied from the litters [14,15,17-24,26,28,29,31,32,34-36,39,42,44,48,50,52-54]. None of the studies reported a sample size calculation or methods for concealment of allocation. Funnel plots of all six outcomes showed symmetrical scattering of the study results around the summary estimate. There was no evidence of a small study effect or publication bias (Supplementary Figure 1).

Plasma glucose after prenatal low protein diet

Twenty-two primary studies provided data for meta-analysis (464 undernourished animals, 464 controls). Twenty-one studies were performed using rats [7-16,18-21,23-29], one using mice [4]. Using the random effects model we found a higher mean plasma glucose

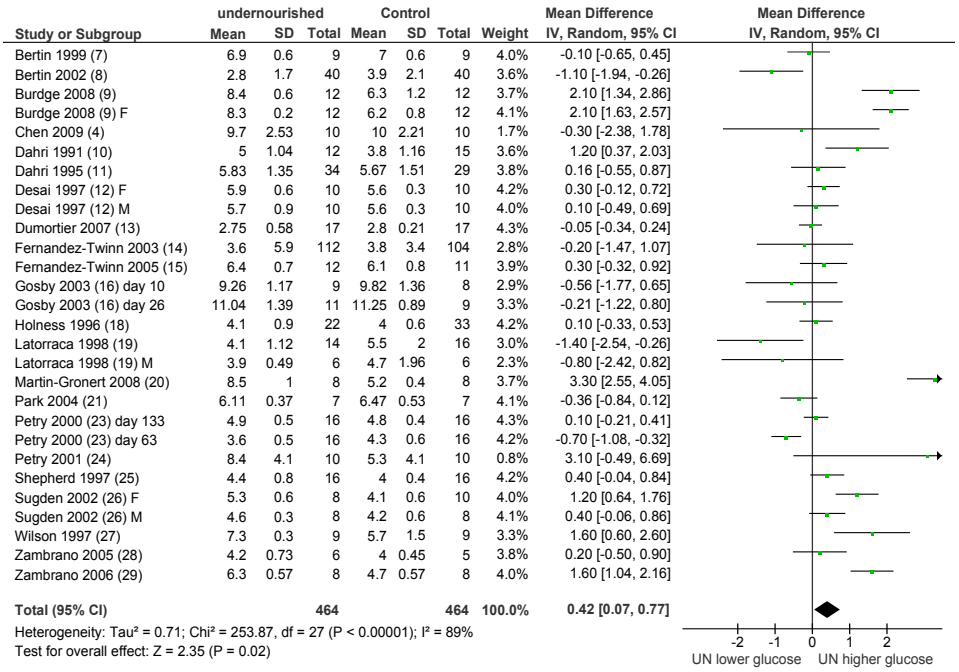

Figure 2: Forest plot of mean differences and 95% CIs in plasma glucose concentrations (mmol/l) after prenatal low protein undernutrition in all animal studies. Study-specific mean differences were combined by using a random-effects model. SD: Standard Deviation; UN: Undernourished.

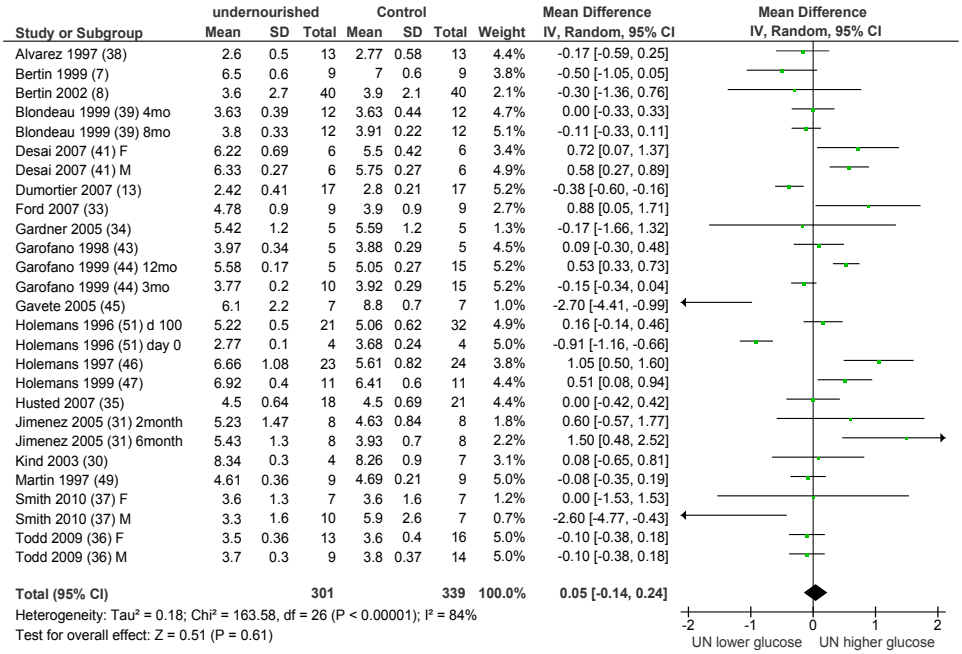

Figure 3: Forest plot of mean differences and 95% CIs in plasma glucose concentrations (mmol/l) after prenatal general undernutrition in all animal studies. Study-specific mean differences were combined by using a random-effects model. SD: Standard Deviation; UN: Undernourished.

level in prenatally undernourished animals compared to the control group: a mean difference of 0.42 mmol/l (95% CI 0.07 to 0.77) (Figure 2). The results showed statistically significant heterogeneity (I^2 89%). The heterogeneity persisted even after separately pooling fasting values, stratifying for the sex of the offspring, or limiting the analysis to Wistar rats only. Offspring of low protein undernourished animals that were older than 6 weeks of age had a 0.54 mmol/l higher plasma glucose level (95%CI 0.16 to 0.92) compared to control offspring. But glucose concentrations measured at day 0 were lower in undernourished offspring compared to controls with a mean difference of -0.62 mmol/l (95% CI -1.34 to 0.11). In both cases, heterogeneity was substantial, with an I^2 of 89% and 69% respectively.

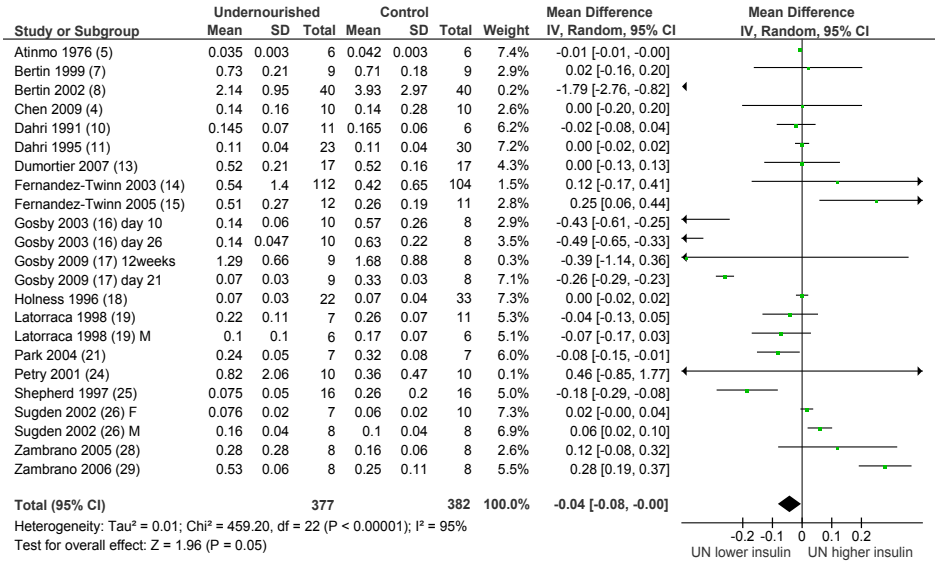

Figure 4: Forest plot of mean differences and 95% CIs in plasma insulin concentrations (nmol/l) after prenatal low protein undernutrition in all animal studies. Study-specific mean differences were combined by using a random-effects model. SD: Standard Deviation; UN: Undernourished.

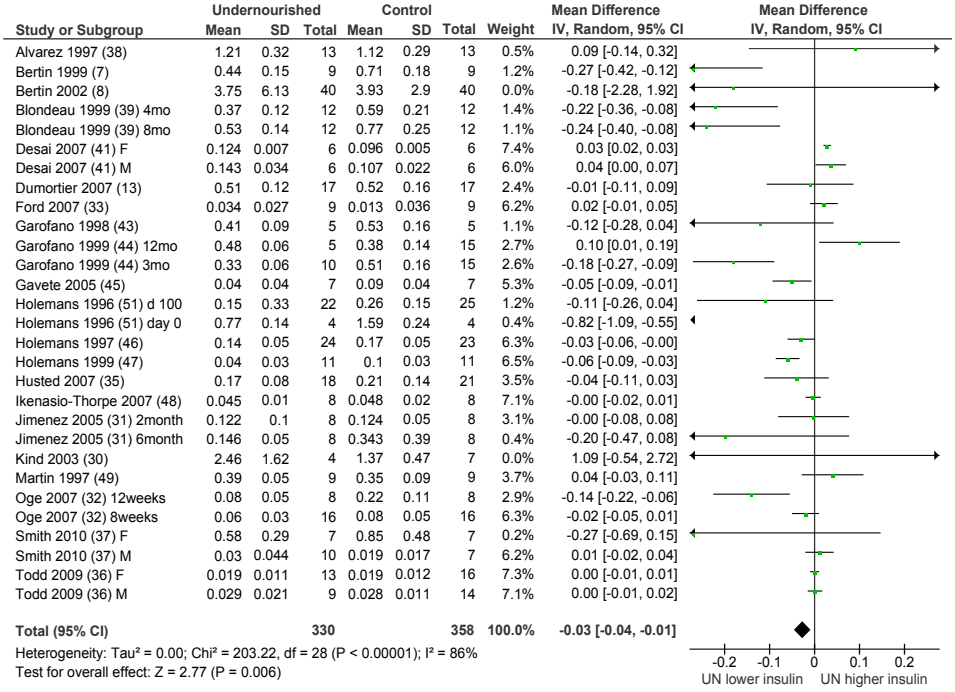

Figure 5: Forest plot of mean differences and 95% CIs in plasma insulin concentrations (nmol/l) after prenatal general undernutrition in all animal studies. Study-specific mean differences were combined by using a random-effects model. SD: Standard Deviation; UN: Undernourished.

Plasma glucose after prenatal general malnutrition

Twenty studies provided data on plasma glucose in offspring after prenatal caloric malnutrition. Twelve studies had been performed in rats [7,8,13,38,39,41,43-47,49,51], one in mice [31], one in guinea pigs [30], and 5 in sheep [33-37]. In total, 301 undernourished animals were studied, compared to 339 controls. The mean plasma glucose level was 0.05 mmol/l higher (95%CI -0.14 to 0.24) in undernourished animals compared to controls (Figure 3). The meta-analysis showed statistically significant heterogeneity (I^2 84%).

Subgroup analysis of rodent models only, stratifying for species, fasting values or sex, did not remove heterogeneity. Undernourished animals measured at day 0 had a significantly lower plasma glucose level, -0.49 (95%CI -0.87 to -0.11) mmol/l (I^2 78%) as opposed to rodents older than 6 weeks, which had a higher plasma glucose level: 0.25 (95% CI 0.04 to 0.46) mmol/l (I^2 79%). Meta-analysis of the effects on sheep only (71 undernourished animals, 79 controls) showed no significant difference in glucose concentrations, with a mean difference of 0.03 mmol/l (95% CI -0.31 to 0.26) (I^2 43%).

Plasma insulin after prenatal low protein

Data for meta-analysis were available from nineteen experimental studies. One study used a pig model [5], one used a mouse model [4], and the remaining 17 studies were performed in a rat model [7,8,10,11,13-19,21,24-26,28,29]. The meta-analysis, using data from 377 protein restricted animals and 382 controls, showed a lower mean plasma insulin level in undernourished offspring compared to control offspring, with a mean difference of 0.04 nmol/l (95% CI -0.08 to 0.00) (I^2 95%) (Figure 4). The heterogeneity persisted after separately pooling animals according to species, sex or age or separately analyzing fasting values.

Plasma insulin after prenatal general malnutrition

In the meta-analysis we could include data from 21 studies, obtained in 330 undernourished animals and 358 controls. Fourteen experiments were conducted in rats [7,8,12,13,38,39,43-49,51], 4 in sheep [33,35-37], 2 in mice [31,32] and one in guinea pigs [30]. The mean plasma insulin level was 0.03 nmol/l lower (95% CI -0.04 to -0.01) in the undernourished group compared to control animals, I^2 86% (Figure 5). The heterogeneity remained after stratification by fasting values, sex, rodent species or age.

In rats at day 0, there was no significant effect of prenatal undernutrition on plasma insulin, with a mean difference of 0.23 nmol/l (95% CI -0.67 to 0.21) (I^2 91%). However, adult undernourished rats had a lower plasma insulin level than controls, with a mean difference of 0.04 nmol/l (95% CI -0.07 to -0.01) (I^2 91%). The four sheep studies (66 undernourished animals, 74 controls) did not show any difference in the mean fasting plasma insulin level (0.00 nmol/l; 95% CI -0.01 to 0.01, I^2 4%) [33,35-37].

Beta cell mass after prenatal low protein

Five rat studies reported beta cell mass of offspring (94 undernourished, 92 control animals) [6-8,13,22]. The beta cell mass was lower in the undernourished offspring compared to control offspring, with a mean difference of -1.24 mg (95% CI -1.88 to -0.60) (Figure 6). There was statistically significant heterogeneity, I^2 97%.

Beta cell mass after prenatal general malnutrition

The 9 studies on rats (91 undernourished and 91 control animals) [7,8,13,38,40,42-44,49] showed a reduction in beta cell mass of 0.44 mg (95% CI -0.75 to -0.13) in undernourished animals compared to controls. The results showed statistically significant heterogeneity (I^2 94%) (Figure 7).

Sensitivity analysis

In a series of sensitivity analysis, we evaluated the robustness of our findings by repeating the analyses a number of times, each time leaving one study out of the meta-analysis. If a study appears to be an outlier, with results very different from the rest of the studies, then its influence will become apparent, as the result without the study would be very much different from the result of the meta-analysis of all the studies. All sensitivity analyses, for each of the six outcome measures evaluated, confirmed the stability of our analysis. No influential individual study could be identified.

Discussion

Although heterogeneity in all meta-analyses was significant, the results generally support the fetal origins hypothesis and show that both general and low protein undernutrition during gestation results

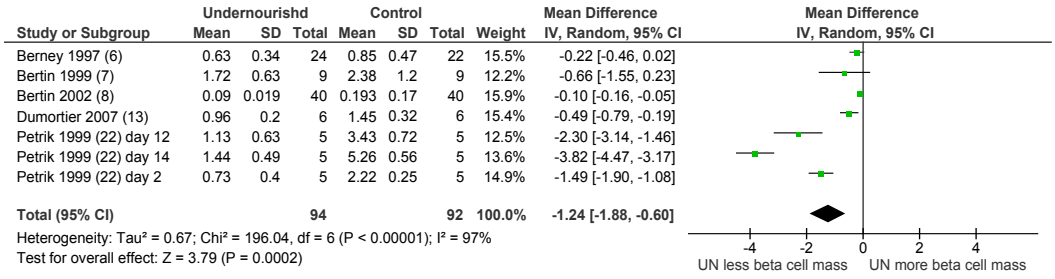

Figure 6: Forest plot of mean differences and 95% CIs in beta cell mass (mg) after prenatal low protein undernutrition in all animal studies. Study-specific mean differences were combined by using a random-effects model. SD: Standard Deviation; UN: Undernourished.

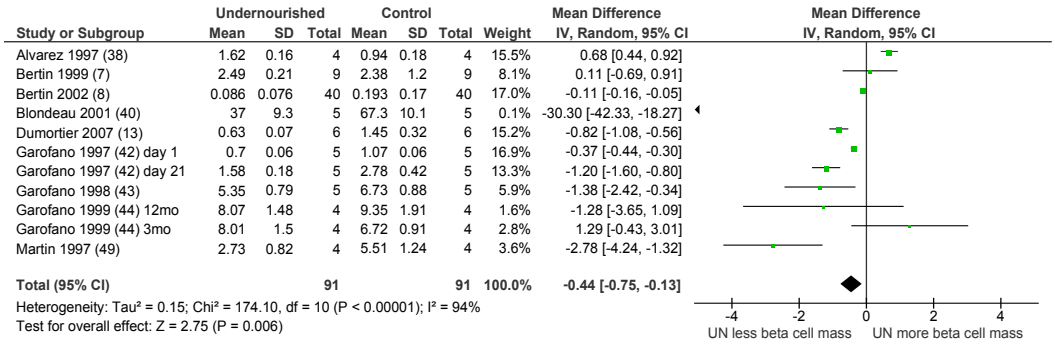

Figure 7: Forest plot of mean differences and 95% CIs in beta cell mass (mg) after prenatal general undernutrition in all animal studies. Study-specific mean differences were combined by using a random-effects model. SD: Standard Deviation; UN: Undernourished.

in increased glucose and reduced insulin concentrations and beta cell mass in the offspring.

Meta-analyses of animal studies are known to show significant heterogeneity [55]. Our findings are in line with this, and we have to be cautious when interpreting the results. There are various sources that could have contributed to the heterogeneity, including the animal mode, species, type of glucose/insulin assay used, quantification method used for assessment of beta cell mass and variations in sample collection and storage, standards and quality control samples and matrix effects will all have contributed to the heterogeneity observed in our meta analyses. We have only been able to explore a few potential sources of heterogeneity, including species, age of the animals at investigation and protocol (fasted or not), and these factors only accounted for a small part of the heterogeneity.

Methodological heterogeneity was one of the major reasons for the heterogeneity observed. The methodological quality of most reported studies was suboptimal, with only one study reporting blinding of the investigators [34], and less than half of the included studies reporting randomization of the animals. None of the studies reported a sample size calculation. In contrast to human studies, randomization, blinding, sample size calculation and planned analysis were not standard. Animal studies that did not report randomization and blinding have been shown to be more likely to report a difference in study groups than studies that did use these methods [55].

The findings from animal research in this review are in line with evidence from human studies, although for ethical reasons obviously these studies cannot be carried out experimentally in humans and therefore are observational in nature. A prospective cohort study in India showed significantly lower cord blood insulin concentrations in babies born from malnourished mothers, compared to controls. In that study malnourishment was defined as a BMI of less than 17 kg/m^2 [56]. In subjects prenatally exposed to the Leningrad siege between 1941 and 1944, there was no difference in concentrations of fasting and 2 hour plasma glucose during an oral glucose tolerance test compared to unexposed subjects. In utero exposed subjects also did not have different plasma insulin concentrations or an excess of known diabetes or glucose intolerance [57].

Three studies have reported on the long term effects of prenatal exposure to the Dutch famine of 1944-45 [58-60]. Glucose tolerance was decreased in subjects that were prenatally exposed to famine when measured at both age 50 and 58 years [58,59]. In a subset of participants, an intravenous glucose tolerance test was performed. The results showed impaired glucose tolerance in prenatally exposed subjects, especially those exposed in mid and early gestation. This effect was suggested to be caused by an insulin secretion defect [60]. Similarly, in adult men and women prenatally exposed to the Chinese famine (1959-1961) there was an increased prevalence of hyperglycemia defined as increased fasting plasma glucose, impaired glucose tolerance or a previous diagnosis of type 2 diabetes [61].

In a recent systematic review of the evidence from animal experiments studying the effects of prenatal undernutrition on later hypertension risk, we found similar results. In general, the results supported the fetal origins hypothesis, fetal undernutrition increased blood pressure levels in the offspring. But here too, heterogeneity was considerable.

In summary, this systematic review shows that the results from animal experiments support the fetal origins hypothesis: prenatal undernutrition leads to a disturbed glucose and insulin metabolism and a decrease in beta cell mass in later life.

Acknowledgement

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Contribution Statement

The authors' responsibilities were as follows: ST, KK, BWM and TR designed the research. MV, DY, ST and RP reviewed the literature and extracted data. MV conducted the statistical analyses and wrote the manuscript. All authors contributed to the revisions of the manuscript and read and approved the final version. None of the authors had any personal or financial conflict of interest.

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