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Early-life Arsenic Exposure, Nutritional Status, and Adult Diabetes Risk

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Abstract

Purpose of Review—*In utero* influences, including nutrition and environmental chemicals, may induce long-term metabolic changes and increase diabetes risk in adulthood. This review evaluates the experimental and epidemiological evidence on the association of early-life arsenic exposure on diabetes and diabetes-related outcomes, as well as the influence of maternal nutritional status on arsenic-related metabolic effects.

Recent Findings—Five studies in rodents have evaluated the role of *in utero* arsenic exposure with diabetes in the offspring. In four of the studies, elevated post-natal fasting glucose was observed when comparing *in utero* arsenic exposure with no exposure. Rodent offspring exposed to arsenic *in utero* also showed elevated insulin resistance in the 4 studies evaluating it as well as microRNA changes related to glycemic control in 2 studies. Birth cohorts of arsenic-exposed pregnant mothers in New Hampshire, Mexico, and Taiwan have shown that increased prenatal arsenic exposure is related to altered cord blood gene expression, microRNA, and DNA methylation profiles in diabetes-related pathways. Thus far, no epidemiologic studies have evaluated early-life arsenic exposure with diabetes risk. Supplementation trials have shown B vitamins can reduce blood arsenic levels in highly exposed, undernourished populations. Animal evidence supports that adequate B vitamin status can rescue early-life arsenic-induced diabetes risk, although human data is lacking.

Summary—Experimental animal studies and human evidence on the association of *in utero* arsenic exposure with alterations in gene expression pathways related to diabetes in newborns, support the potential role of early-life arsenic exposure in diabetes development, possibly through increased insulin resistance. Given pervasive arsenic exposure and the challenges to eliminate arsenic from the environment, research is needed to evaluate prevention interventions, including the possibility of low-cost, low-risk nutritional interventions that can modify arsenic-related disease risk.

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Conflict of Interest

Ana Navas-Acien, Miranda J. Spratlen, Ahlam Abuawad, Nancy J. LoIacono, Anne K. Bozack and Mary V. Gamble declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Arsenic; Diabetes; Early-life exposures; Nutrition; One-carbon metabolism

Introduction

In utero exposures may induce long-term metabolic changes and increase diabetes risk in adulthood, as supported by the concept of *Developmental Origins of Health and Disease*.[1-3] Arsenic, a non-essential chemical element, found ubiquitously in the environment through both naturally occurring and commercial or industrial processes, is a major contaminant in water and food worldwide. Exposure to arsenic has been associated with the development of certain cancers, including lung, skin and bladder cancer, cardiovascular disease, skin lesions, diabetes and neurodevelopmental deficits.[4-11] Prenatal arsenic exposure has been related to altered gene expression in diabetes pathways in newborns.[12-16] In rodent models, prenatal arsenic induces diabetes in adult offspring.[17-21] It is also known that maternal nutrition during pregnancy influences programming for adiposity and diabetes risk in adult life. For instance, an imbalance in B vitamins during pregnancy has been related to increased central adiposity and diabetes risk in several populations.[22-25] In randomized clinical trials, folic acid supplementation increases arsenic methylation which facilitates its excretion through the urine and reduces blood arsenic levels[26-28]. Furthermore, folate sufficiency has been related to reduced arsenic-related toxicity[26-28] The objective of this review is to evaluate the experimental and epidemiological evidence available on the association of early-life arsenic exposure with diabetes and diabetes-related outcomes, as well as the influence of maternal nutritional status on arsenic-related metabolic effects. An additional objective is to identify research gaps with a particular focus on informing the development of interventions to prevent and mitigate the long-term effects of early-life arsenic exposure.

Methods

This review summarizes epidemiologic and experimental evidence on the role of arsenic and diabetes with a focus on the evidence available for early-life exposure, and the potential modifying role of B vitamin nutritional status. We first review experimental studies on early-life arsenic exposure and diabetes in the offspring. Second, we review evidence on arsenic and epigenetic programming *in utero* focusing on pathways that are particularly relevant for metabolic development and diabetes. Third, we summarize the evidence and discuss the potential role of B vitamin nutritional status in modifying the diabetogenic effects of arsenic. Finally, we discuss the research needs for general populations. The manuscripts identified for this review have been compiled over many years by the study investigators through systematic reviews and ongoing systematic searches of the literature using both free text and indexed terms including arsenic, arsenite, arsenate, methylated arsenic species, arsenic poisoning, diabetes, metabolic syndrome, B vitamins, one-carbon metabolism, and folate.

Experimental Studies of Early-Life Arsenic Exposure and Diabetes

Five studies (three in mice, two in rats) have evaluated the role of *in utero* arsenic exposure with diabetes in the offspring (Table 1).[17-21] Two studies included a pre-mating exposure

period and three studies included a post-birth exposure period (one of them splitting the litter to compare *in utero* only vs. both *in utero* and post-birth). All studies included a comparison group with no *in utero* exposure. Comparing *in utero* arsenic exposure with no exposure, elevated post-natal fasting glucose was observed in four of the five studies, although some studies found this association in males or females only, with no consistent pattern by sex. In the four studies evaluating the homeostatic model assessment (HOMA), a measurement of insulin resistance, the offspring exposed to arsenic *in utero* showed elevated HOMA levels compared with unexposed offspring.[17-20] *In utero* arsenic exposure also resulted in positive histological scores for non-alcoholic fatty liver disease (NAFLD), which is tightly linked to insulin resistance, in the two studies evaluating this outcome.[21] Overall, these experimental studies support that *in utero* arsenic exposure influences the early programming of diabetes and related complications later in life. Although these animal experiments are compelling and support that early-life arsenic exposure might contribute to the development of diabetes in adulthood, there are substantial limitations to generalizing from animal models to humans.[29,30] Epidemiologic evidence is thus critical to address translation of these findings to human populations.

Epigenetic Reprogramming *In Utero*

It is now well established that both malnutrition and exposure to numerous environmental chemicals during pregnancy can induce persistent alterations of gene expression resulting in metabolic disorders in adulthood,[31-36] potentially through epigenetic reprograming.[36-38] Specifically for arsenic, *in utero* exposure has been shown to induce microRNA (miRNA) changes related to glycemic control in mice and rat models.[39,40] Several birth cohorts of arsenic-exposed pregnant mothers in New Hampshire, Mexico, and Taiwan have shown that increased prenatal arsenic exposure is related to altered cord blood gene expression, miRNA, and DNA methylation profiles in diabetes-related pathways (Akt signaling pathway, miRNAs miR-107, and miR-20b).[12-16] In a Mexican birth cohort, arsenic exposure *in utero* was related to differential methylation of *KCNQ1*, an imprinted gene that is related to diabetes.[14] In a mouse model, the combination of high chow folate (11 mg/kg) with water inorganic arsenic exposure (85 mg/L) from gestational days 8 to 15 resulted in lower birth weight and epigenetic changes in numerous genes including those known to be imprinted, when compared with standard chow folate (2.2 mg/kg) and no arsenic exposure.[41] While these findings could indicate an adverse response of combined folate and inorganic arsenic exposure, in the absence of health endpoints, whether this epigenetic response is positive or negative is unknown. Also, the high folate and high inorganic arsenic exposure limit the extrapolation of these findings to human populations. Overall, these findings on arsenic-related epigenetic changes in utero provide potential mechanisms whereby early-life arsenic exposure can induce adult metabolic outcomes.

Limited Epidemiologic Evidence for Early-Life Arsenic Exposure and Diabetes

A number of recent reviews have summarized ecological studies, from Chile and Japan, on the association of high (>100 μg/L), early-life arsenic exposure with cancer, cardiovascular

disease (CVD), and respiratory disease incidence and mortality.[29,36,38,42-45] However, assessment of diabetes in these ecological studies is lacking. Longitudinal assessment of early-life arsenic exposure and latent disease risk, including cardiometabolic outcomes, is limited. Prospective studies from Bangladesh[43] and Taiwan[46] have shown associations between moderate to high early-life arsenic exposure with blood pressure and lipid metabolism, respectively, in childhood and adolescence. In a case-control study on the prevalence of diabetes in US children and adolescents, arsenic metabolism, but not arsenic exposure (measured in plasma), was associated with type II diabetes.[47] However, there are currently no epidemiologic studies evaluating the association of early-life arsenic exposure with diabetes development. Investigating the link between early-life arsenic exposure and incident diabetes in populations exposed to a wide range of arsenic exposure levels is thus an important research need.

Early-life One-Carbon Metabolism Nutritional Status, Arsenic Exposure, and Diabetes Risk

One-carbon metabolism (OCM) is a biochemical pathway (Fig. 1) that is essential for the synthesis of the universal methyl donor, S-adenosylmethionine (SAM).[48] This pathway is dependent on B vitamins, including vitamins B12, B6, riboflavin, and folate; in turn, deficiencies in these nutrients may result in impaired OCM.[48] Dietary folate, in the form of 5-methyltetrahydrofolate (5mTHF), can donate a methyl group for the remethylation of homocysteine (Hcys) to form methionine which can subsequently be activated to form SAM.[49] Elevated plasma Hcys is a sensitive indicator of impaired OCM and related nutrient deficiencies. SAM is needed in cellular signaling; protein, lipid, and carbohydrate metabolism; and methylation of arsenic, DNA, and numerous other substrates.[50] In Bangladesh, supplementation with folic acid, an oxidized form of folate which is reduced to 5mTHF, increased arsenic methylation and lowered blood arsenic.[26-28] Observational epidemiological studies from Mexico,[51] the USA,[52-54] and Bangladesh[55] have also reported associations between dietary intake of other OCM-related B vitamins and arsenic methylation efficiency. SAM-dependent methylation reactions generate S-adenosylhomocysteine (SAH) which is hydrolyzed to Hcys. Homocysteine can either be remethylated or directed to the transsulfuration pathway; the latter is critical for the synthesis of glutathione (GSH), the most abundant endogenous antioxidant. GSH redox state influences the regulation of SAM-synthetase as well as of arsenic metabolism.[56,57]

The importance of OCM-related micronutrients for mitigating arsenic toxicity in adults and in early-life have recently been reviewed.[26,58] and has been demonstrated in experimental studies for diabetes-related outcomes. In mice, hyperglycemia in the offspring, induced by *in utero* exposure to water arsenic, was rescued by maternal supplementation with folate+B12 (Fig. 2).[20] In 3-week old mice exposed to 100 μg/L water arsenic, insulin resistance was only observed in the presence of both low folate and a high fat diet.[59] This scenario of arsenic exposure in the presence of low folate replicates dietary patterns in many human populations. For example, in the Strong Heart Family Study, a prospective cohort study in American Indian communities, a diet high in fat content (e.g., high red meat intake) but low in B vitamin intake, in particular low folate (e.g., lack of vegetables), is common.[53,60,61]

Also, while most of the current arsenic levels in drinking water in this study are below 10 μg/L (the US EPA safety standard), this population's arsenic exposure *in utero* was markedly higher. This is because historically, prior to the year 2000, when the cohort was recruited, water arsenic levels persistently exceeded 10 μg/L for decades.[62] Still even with the current moderate arsenic exposure in this population, an increased risk of diabetes with higher arsenic exposure has been observed (hazard ratio of 1.57 [95% CI 1.18, 2.08] per interquartile range of urinary arsenic [7.2 versus 2.9 μg/g creatinine] among 1,376 participants free of diabetes and pre-diabetes at baseline).[10]

Birth cohort studies have shown that an imbalance in OCM-related micronutrients during pregnancy may predispose offspring to adiposity and diabetes risk. Much of this work is based on South Asian populations, where low maternal vitamin B12 and high folate have been related to offspring visceral fat and insulin resistance.[22-25] In the Strong Heart Study, because of a diet comprised of relatively high meat products and low vegetable intake, the imbalance in OCM-related micronutrients is characterized by low folate and high vitamin B12 (Fig. 3). Whether this imbalance is also related to increased offspring visceral fat and insulin resistance is currently unknown. This is a relevant hypothesis to test, as the imbalance in OCM status can be easily modified through dietary interventions.

Associations between OCM, arsenic, and diabetes have also been studied in the context of arsenic metabolism. After absorption, inorganic arsenic is metabolized, with substantial inter-individual variation, to mono- and di-methylated arsenicals (MMA, DMA) in a process that facilitates arsenic excretion in urine.[56,63-70] Higher urine MMA% and lower DMA% are associated with higher risk of cancers of the lung, bladder, breast, and skin and with CVD.[71-78] For diabetes outcomes, however, the patterns of association appear to be strikingly different.[79] For example, in the Strong Heart Study, participants having lower MMA%, and higher DMA% at baseline had a higher rate of incident diabetes and MetS, and higher insulin resistance over a 10-year period.[80] Cross-sectional studies from Bangladesh[81] and Mexico[82] also reported a positive association between DMA% and diabetes. This surprising association between DMA% and diabetes may be influenced by OCM status. In a US-based pilot targeted metabolomics study (n=59), eight metabolites (all OCM-related) were associated with both arsenic methylation and diabetes outcomes, and the association between arsenic metabolism and diabetes markers were markedly attenuated after accounting for these OCM metabolites.[83] However, this was a small cross-sectional study that could not formally test for mediation, confounding or reverse causality. Research is needed to understand the role of OCM status in both arsenic exposure and arsenic metabolism, preferably in longitudinal studies that can also account for the role of early-life nutritional and arsenic exposure status.

Research Needs and Conclusions

Compelling experimental and epidemiologic evidence on the association of *in utero* arsenic exposure with alterations in gene expression pathways related to diabetes in newborns support the possible role of early-life arsenic exposure in diabetes development, maybe through increased levels of visceral adiposity and insulin resistance. A major limitation of the evidence is the lack of epidemiologic studies linking early-life arsenic exposure with

adult-onset diabetes in the offspring. Also, while there is evidence on the possible role of an imbalance of OCM-related B vitamins in adiposity and insulin resistance, as well as on the role of these micronutrients in arsenic methylation and toxicity, whether OCM-related B vitamin status during early-life plays a role in arsenic-related diabetes is unknown. Understanding the role of early-life versus adult arsenic exposure on diabetes risk is needed to inform risk assessment and for planning prevention interventions. Current risk assessment for inorganic arsenic has not considered whether exposure to arsenic during pregnancy and the first years of life has a different impact on health outcomes compared with exposure during adulthood. Given pervasive arsenic exposure and the challenges to eliminate arsenic from the environment, there is a need to evaluate prevention interventions, including the possibility of low-cost, low-risk nutritional interventions that can modify arsenic-related disease risk.

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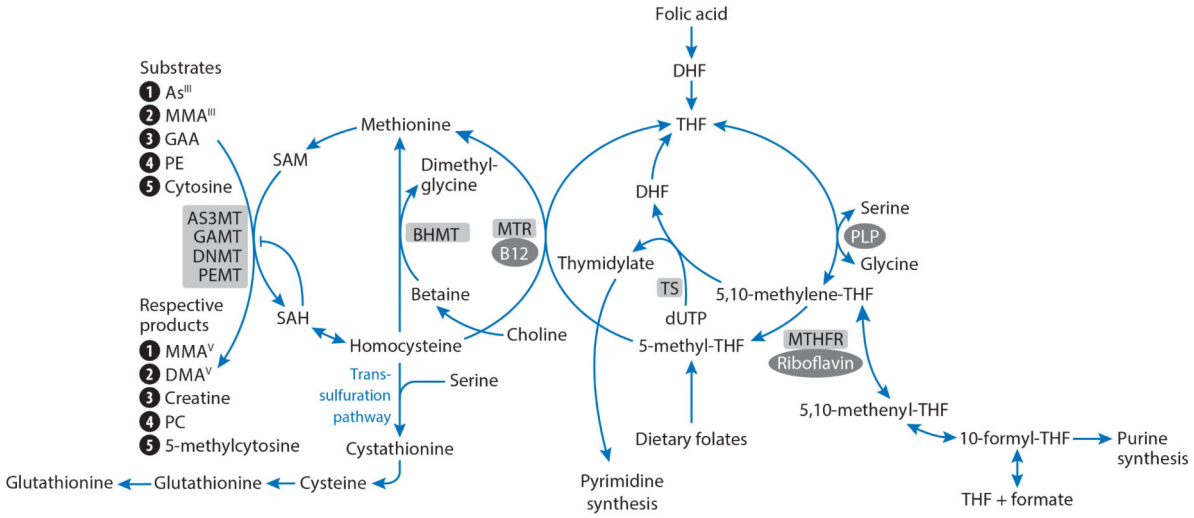

Fig 1. One-carbon metabolism.

Folic acid is reduced to dihydrofolate and tetrahydrofolate (THF). A one-carbon unit is transferred from serine to THF to form 5,10-methylene-THF which is used for thymidylate synthesis or reduced to 5-methyl-THF. Dietary folate can enter one-carbon metabolism as 5-mTHF. The one-carbon unit is transferred to homocysteine by methionine synthase using the cofactor vitamin B12, forming methionine and THF. Homocysteine can also be remethylated using betaine as the methyl donor. Methionine is activated to S-adenosylmethionine (SAM), which serves as the methyl donor for reactions including arsenic methylation. Methylation reactions generate the methylated product and S-adenosylhomocysteine (SAH), an inhibitor of methyltransferase enzymes. SAH is hydrolyzed to homocysteine, and can be remethylated or be used in the transsulfuration pathway.

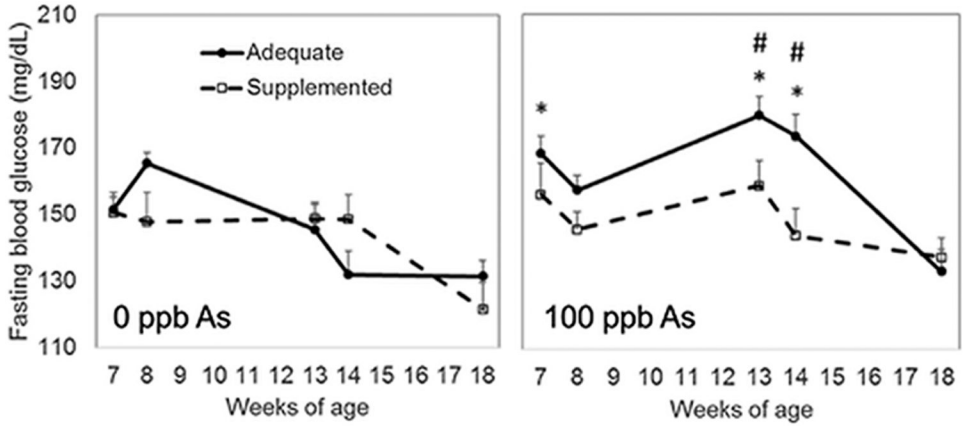

Fig 2. Folate/B12 supplementation.

Diets supplemented with higher folate + vitamin B12 supplementation rescued elevated fasting glucose levels induced by arsenic *in utero* as compared with an adequate (normal) diet. (Adapted from Huang et al.)[20].

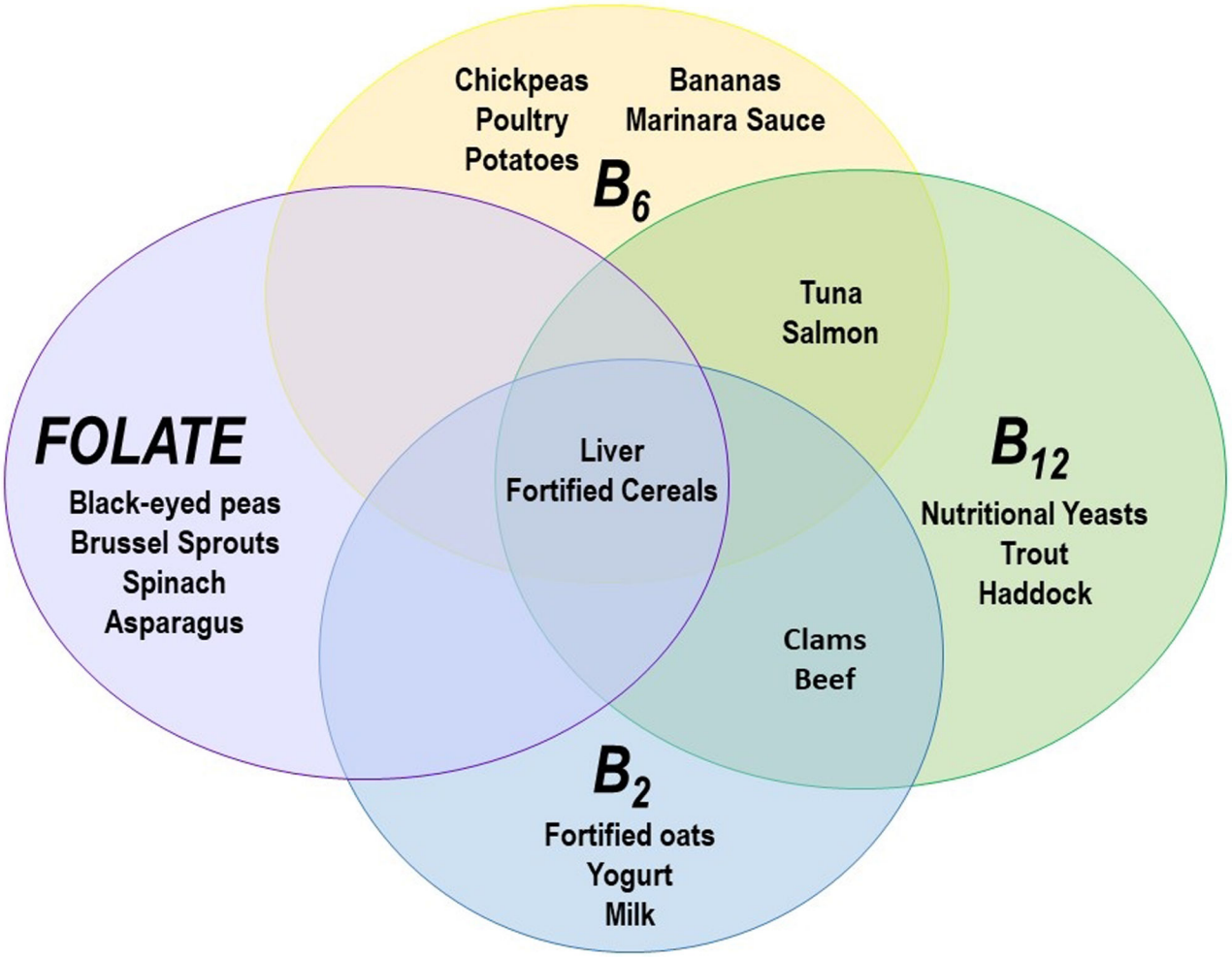

Fig 3. Major dietary sources of one-carbon metabolism (OCM) related nutrients.

Foods listed under OCM nutrients are considered to be high dietary sources of that nutrient (provide 20% or more of the daily value). (Modified from Spratlen MJ et al.)[53].

Table 1.

Experimental animal studies of early-life arsenic (As) exposure and diabetes-related outcomes

1st author, year	Animal Model (diet)	Water As Dose (mg/L)	Exposure Period			Diabetes-related outcomes	Results (age and sex offspring)
			Pre-mating	In-utero	Post-birth		
Davila-Esqueda, 2011	Wistar rats (standard chow)	0, 3	Yes	Yes	Yes	FPG, GTT, HbA1c, pancreatic insulin, HOMA-IR, HDL-c, TGL	↑FPG, ↑GTT, ↑HbA1c, ↑pancreatic insulin, ↑HOMA-IR, ~HDLc, ~TGL (4 mo old F, not in M)
Sanchez- Soria, 2014	Webster mice (standard chow)	0, 0.1	No	Yes	No	FPG, HDL-c, TGL, NAFLD	↑FPG, ↑HDL-c, ~TGL, NFALD +2 score (4, 8 mo. old F and M)
Ditzel, 2016	Webster mice (western-style)	0, 0.1	No	Yes	No/Yes *	FPG, HbA1c, HOMA-IR, TGL, NAFLD, metabolomics (337 compounds)	↑FPG, ↑HbA1c, ↑HOMA-IR, ↑TGL, NAFLD+4/+6, alterations in glycolysis and liver metabolites (13 wk. old F, M)
Bonaventura, 2017	Sprage-Dawley rats (standard chow)	0, 5, 50	No	Yes	Yes	FPG, GTT, pancreatic insulin, HOMA-IR	~FPG, ~GTT, ↑ pancreatic insulin (M, F), ↑HOMA-IR (F) (4, 8 wk)
Huang, 2018	C57BL/6J mice (AN93G w/wo folate/B12 suppl.)	0, 0.1, 1	Yes	Yes	No	FPG, GTT, plasma insulin, HOMA-IR	↑FPG (M **), ~FPG (F), ~GTT (M, F), ↑plasma insulin (M **), ↑HOMA-IR (M **) (8, 14 wk old)

* Litters were split in 2 groups, one with/one without arsenic exposure post-birth.

** Significant results found for those with an adequate diet.

F: female, FPG: fasting plasma glucose, GTT: glucose tolerance test, HbA1C: hemoglobin A1C, HDL-c: high-density lipoprotein cholesterol, M: male, mo: month, NAFLD: non-alcoholic fatty liver disease, TGL: triglycerides, wk: week.