Paternal metabolic and cardiovascular programming of their offspring: A systematic scoping review

Claudia Eberle, Michaela F. Kirchner, Raphaela Herden, Stefanie Stichling

Medicine with Specialization in Internal Medicine and General Medicine, Hochschule Fulda–University of Applied Sciences, Fulda, Germany

* claudia.eberle@hs-fulda.de

Abstract

Background
There is lots of evidence that maternal peri-gestational metabolic, genomic and environmental conditions are closely linked to metabolic and cardiovascular outcomes in their offspring later in life. Moreover, there is also lots of evidence that underlying mechanisms, such as molecular as well as epigenetic changes may alter the intrauterine environment leading to cardio-metabolic diseases in their offspring postnatal. But, there is also increasing evidence that cardio-metabolic diseases may be closely linked to their paternal metabolic risk factors, such as obesity, Type 2 Diabetes and other risk factors.

Objective
To analyse the evidence as well as specific risk factors of paternal trans-generational programming of cardio-metabolic diseases in their offspring.

Methods
Within a systematic scoping review, we performed a literature search in MEDLINE (PubMed) and EMBASE databases in August 2020 considering original research articles (2000–2020) that examined the impact of paternal programming on metabolic and cardiovascular offspring health. Epidemiological, clinical and experimental studies as well as human and animal model studies were included.

Results
From n = 3,199 citations, n = 66 eligible studies were included. We selected n = 45 epidemiological as well as clinical studies and n = 21 experimental studies. In brief, pre-conceptional paternal risk factors, such as obesity, own birth weight, high-fat and low-protein diet, undernutrition, diabetes mellitus, hyperglycaemia, advanced age, smoking as well as environmental chemical exposure affect clearly metabolic and cardiovascular health of their offspring later in life.
Conclusions
There is emerging evidence that paternal risk factors, such as paternal obesity, diabetes mellitus, nutritional habits, advanced age and exposure to environmental chemicals or cigarette smoke, are clearly associated with adverse effects in metabolic and cardiovascular health in their offspring. Compared to maternal programming, pre-conceptual paternal factors might also have a substantial effect in the sense of trans-generational programming of their offspring and need further research.

Introduction
Evidence suggests that maternal metabolic, molecular genomic and environmental conditions might imprint metabolic and cardiovascular conditions in their offspring [1–6]. Hence, pathophysiological changes in intrauterine environment might “program” and predict those developments in the offspring early on [5]. In this context, trans-generational programming describes the perturbation at critical periods of development causing permanent lifelong alterations with irreversible consequences [1]. Hales and Barker’s “thrifty phenotype hypothesis” [7] is stating “that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes mellitus and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism” [7]. Further, the “Predictive Adaptive Responses Hypothesis” outlines that the fetus predicts the postnatal environment by “adapting” developmental processes in utero [1]. Whereas an altered fetal environment through maternal influences is very likely associated with the development of metabolic and cardiovascular diseases in later life, less is known about paternal factors influencing offspring health [8]. Hence, the “advanced fetal programming hypothesis” proposes that programming events related to paternal genes are affecting the fetal phenotype independently of the fetal genome [9]. According to that hypothesis, paternal environmental factors (e.g. body composition, endocrine function, nutritional habits, and age) might influence the offspring’s phenotype through epigenetic imprinting processes in sperm as the alterations in the paternal germline epigenome are passed on to the offspring [8–11]. Paternal under- and overnutrition can induce metabolic phenotypes in the offspring, and the induced phenotype can affect multiple generations [12]. The transfer of metabolic disease risk through male parentage implies an inheritable factor carried by sperm. Sperm-based transmission offers a comprehensible system for querying heritable epigenetic factors that influence the metabolism [12].

We conducted a systematic scoping review to summarize the updated evidence. We aimed at reviewing the existing evidence on whether and which paternal risk factors affect trans-generational programming and thus lead to adverse metabolic and cardiovascular outcomes in offspring. Then, we discuss the impact of paternal compared to maternal programming.

Materials and methods
Data sources, search and screening strategy
We performed a systematic scoping review to summarize the evidence available on the topic for the purpose of identifying potential paternal risk factors and different cardio-metabolic outcomes, outlining evidence gaps, reviewing various types of evidence and conveying the breadth of the topic [13]. This review combines systematic and scoping approaches using
systematic, explicit methods to explore and describe a broad evidence base. We followed PRISMA for systematic reviews [14] (S1 Checklist) and Joanna Briggs Institute for systematic scoping reviews guidelines [13].

The electronic databases MEDLINE (PubMed) and EMBASE were searched in August 2020 using the following keywords as Medical Subject Headings and Embase Subject Headings terms and title/abstract terms:

- MEDLINE (PubMed): ((((((parental[Title/Abstract]) OR (paternal exposure[MeSH Terms])) OR (male’[Title/Abstract]) OR (father’[Title/Abstract])) OR (paternal’[Title/Abstract])) AND (((((preconception[Title/Abstract]) OR (prenatal[Title/Abstract])) OR (transgenerational[Title/Abstract])) OR (fetal development[MeSH Terms])) OR (programming’[Title/Abstract]))) OR (cardiovascular disease[MeSH Terms]) OR (metabolic disease[MeSH Terms])) AND ((english[Filter] OR german[Filter]) AND (2000:2020[pdat]))

- EMBASE: (((("paternal":ti,ab) OR ("parental":ti,ab) OR ("male":ti,ab) ("father":ti,ab) ("paternal exposure"/exp)) AND ("transgenerational":ti,ab) OR ("programming":ti,ab) OR ("fetus development"/exp OR ("preconception":ti,ab) AND ("cardiovascular disease"/exp OR ("metabolic disorder"/exp))) AND ((embase)/lim AND (english)/lim OR (german)/lim) AND (2000–2020/py))

After database searching and elimination of duplicates, records were screened by title and abstract. Then, studies with full-text were screened and eligible publications were selected for inclusion. In addition, the reference lists of included studies were manually checked to identify further publications. No protocol has been published and two independent reviewers selected the publications.

**Eligibility criteria**

Peer-reviewed studies with full-text including original data on the impact of paternal risk factors (e.g. obesity, diabetes mellitus, nutrition, smoking) on metabolic and cardiovascular programming in offspring were involved. We included studies published over the past 20 years (January 2000 until August 2020) in English and German. To encourage our scope, we included epidemiological (cross-sectional, cohort, case-control studies), clinical and experimental trials as well as animal model and human studies. We excluded reviews and meta-analyses as well as editorials, conference abstracts, letter, notes, and comments.

**Data extraction and synthesis**

We extracted the following information: author, publication date, study design, study population, paternal risk factors, cardio-metabolic outcomes (offspring), and main findings. P-values below 0.05 were considered statistically significant. Furthermore, P-values were taken unchanged from the papers. First, studies were synthesized according to epidemiological and clinical designs (1) and experimental designs (2). Second, they were organized regarding the paternal factors examined:

1. **Epidemiological and clinical studies**: BMI/obesity, birth weight, nutrition, diabetes mellitus, age, smoking and environmental chemical exposure.

2. **Experimental studies**: high fat diet and obesity, low protein diet, undernutrition, hyperglycemia, and environmental chemical exposure.
With the aim of providing an overview of the existing evidence regardless of quality, we have not carried out a formal quality assessment in compliance with the guidelines for systematic scoping reviews [13].

Results
In total, n = 3.325 citations were identified. After the removal of the duplicates, n = 2.876 articles were screened by title and abstract, which led to the exclusion of n = 2.791 publications. We screened n = 85 studies with full-text for eligibility. After manual research of reference lists (n = 9 studies identified [15–21]), n = 66 studies were finally included in this systematic scoping review. We selected n = 45 epidemiological and clinical studies and n = 21 experimental studies. The search and selection process is shown in Fig 1. An overview of study characteristics is provided in S1 File.

Table 1 summarizes selected paternal programming effects and the distinction between female and male offspring.

**Paternal risk factors: Epidemiological and clinical studies**

**BMI and obesity.** Chen et al. (2012) [22] (examining n = 899 newborns) demonstrated that the paternal BMI correlated with the birth parameters of male, but not female offspring concluding that the paternal BMI presents a risk factor for cardiovascular diseases in male adult offspring [22].

Sørensen et al. (2016) [20] reported a significant association between the pre-conceptional parental BMI and the BMI of the children at birth, 12 months and 7 years of age. The results showed that the association between anthropometrics of the mother and those of the offspring is stronger than between father and offspring. However, the differences diminished with advancing offspring age, becoming minor at 7 years of age [20]. In addition, Zalbahar et al. (2016) [19] found a positive association between paternal BMI and BMI and waist circumference (WC) in adult offspring.

Gaillard et al. (2014) [27] showed that paternal pre-conceptional BMI contributed to an adverse cardiometabolic profile in consecutive generations by showing a significant positive association between paternal and childhood BMI [27]. Offspring of obese fathers showed higher values of total body and abdominal fat mass as well as higher triglyceride, insulin and C-peptide levels in comparison to offspring from fathers with normal weight [27]. Similar findings were reported by McCarthy et al. (2015) [28] finding a significant positive association between paternal BMI and BMI, WC, and triglyceride levels of the offspring. Santos Ferreira et al. (2017) [16] and Labayen et al. (2010) [29] also found that both maternal and paternal BMI could be linked to a detrimental cardiometabolic profile in later life of the offspring.

A study by Magnus et al. (2018) [30] indicated that maternal and paternal pre-conceptional obesity was clearly associated with an increased risk of developing type 1 diabetes in the childhood. Within a prospective cohort study, Veena et al. (2013) [31] found that maternal and paternal obesity showed a positive correlation to obesity and fasting insulin concentrations in offspring [31]. Paternal obesity was associated with an increased childhood BMI and WC, a higher sum of skin folds, an elevated body fat percentage, and led to higher offspring fasting blood glucose levels and the development of an insulin resistance [31].

Soubry et al. (2013) [32] determined clear associations between pre-conceptional obesity and DNA methylation patterns of the imprinted Insulin-Like Growth Factor 2 (IGF2) in the offspring. They found a significant decrease in methylation at the differentially methylated regions (DMRs) of the IGF2 gene among newborns of obese fathers [32] and identified an inverse relationship between DNA methylation in offspring and paternal obesity. As low
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097

For more information, visit www.prisma-statement.org.

Fig 1. Flow diagram of the literature search and selection.

https://doi.org/10.1371/journal.pone.0244826.g001
methylation at this DMR had already been linked with negative health outcomes, the authors assumed a pre-conceptional impact of paternal adiposity on the reprogramming of imprint marks during spermatogenesis [32].

**Birth weight.** McCowan et al. (2011) [33] (investigating n = 2002 couples) demonstrated that men who fathered SGA infants (= defined as a weight below the 10th percentile for the gestational age) showed actually lower birth weights than men who fathered non-SGA infants [33]. Therefore, birth size appears to be heritable through the paternal germ line. However, McCowan et al. could not confirm a strong inverse association between paternal birth weight and paternal obesity. Rather, the authors noted under consideration of varied populations that the relationship between birth weight and obesity in adulthood differed depending on gender and age [33]. Furthermore, Derraik et al. (2019) [34] reported that the likelihood of having an baby, which is large for gestational age (LGA), increased with a higher paternal birth weight and the father being tall [34].

**Nutrition and nutritional habits.** Kaati et al. (2002) [35] showed that if the father was exposed to a famine during his slow growth period, the offspring were protected against deaths caused by cardiovascular diseases. If the paternal grandfather experienced a famine during his slow growth period, the grandchildren tended to be safe from developing diabetes [35]. In contrast, if the paternal grandfather had access to a surfeit of food during their slow growth period, their grandchildren had a fourfold higher risk of dying from diabetes. Also, the food supply of the paternal grandfather could only be linked to the mortality of their grandsons, whereas the granddaughter’s mortality was associated with the paternal grandmother’s food supply [35].

According to Li et al. (2017) [36], at the exposure of famine, there was a significant increase in the risk of developing hyperglycemia and Type 2 Diabetes mellitus (T2DM) in adult offspring of the first generation, and the hyperglycemia risk increased significantly in the second generation, whereas a significantly increased risk of T2DM could not be confirmed [36].

**Diabetes mellitus.** Penesova et al. (2010) [37] demonstrated that fathers with an onset of diabetes before the age of 35 had leaner children, which further showed a decreased early insulin secretion [37]. Silva et al. (2017) [38] support this hypothesis as the authors were able to

| Paternal Risk Factor | Offspring | Main Findings | p-value |
|----------------------|-----------|---------------|---------|
| BMI                  | Female    | Paternal BMI could not be associated with birth parameters of female offspring [22] | 0.224 |
|                      | Male      | Paternal BMI was associated with birth weight in male offspring [22] | 0.006 |
| Nutrition            | Female    | Female offspring of high-fat diet fed fathers were heavier than offspring in control group, gained more weight and were insulin resistant [23] | <0.05 |
|                      |           | Female offspring of obese fathers, induced by HFD, showed adiposity and insulin resistance; further, the females presented a reduced β-cell and islet area [24] | 0.09 |
|                      | Male      | Male offspring of diet restricted fathers showed reduced fat mass, but an increased number of adipocytes, increased circulating lipids and free fatty acids; at 14 weeks insulin sensitivity was improved [25] | <0.05 |
| Diabetes mellitus    | Female    | Positive association between a paternal history of diabetes and prediabetes in female offspring [26] | 0.038 |
|                      | Male      | No significant association could be determined between a diabetic father and prediabetes in male offspring [26] | 0.162 |
| Smoking              | Female    | Early-onset paternal smoking was not significantly associated with female offspring BMI [21] | 0.587 |
|                      | Male      | Paternal mid-childhood smoking is significantly associated with an increased BMI in boys at 9 years [21] | 0.015 |
| Age                  | Female    | No significant influence of paternal age on female offspring regarding the function of the Renin-Angiotensin-Aldosterone-System or the pituitary-adrenal axis [22] | 0.339 |
|                      | Male      | Paternal age has a significant influence on key hormone systems for cardiovascular diseases in male offspring (e.g. Renin-Angiotensin-Aldosterone-System or pituitary-adrenal axis) [22] | 0.138 |

P-values below 0.05 were considered statistically significant.

https://doi.org/10.1371/journal.pone.0244826.t001
clearly link T2DM to an increased offspring BMI and elevated triglyceride levels. Wang et al. (2015) [39] also found a clearly positive association between parental diabetes and T2DM incidence in offspring. T2DM incidence in overweight subjects showed a stronger association with paternal than with maternal diabetes [39].

In the study by Praveen et al. (2012) [40], the offspring with a family history of T2DM showed clearly higher BMI values and higher plasma insulin, C-peptide and proinsulin levels as well as lower insulin sensitivity and β-cell compensation in the offspring [40]. There were no significant differences between offspring of diabetic mothers and those of diabetic fathers [40].

Furthermore, Linares Segovia et al. (2012) [41] reported the highest BMI values of the offspring in families, in which both parents were diabetic, whereas the lowest glucose and total cholesterol levels were determined in offspring of healthy parents. Almari et al. (2018) [26] outlined that parental history of diabetes did not clearly increase the prevalence of prediabetes, but parental history of diabetes in addition to obesity in offspring [26]. Maternal diabetes was solely related to prediabetes among male offspring [26]. Shields et al. (2006) [42] demonstrated that paternal insulin resistance influenced the umbilical cord insulin concentrations in a way which was clearly contributing to the development of a fetal insulin resistance, independent of maternal factors [42].

In addition, Myklestad et al. (2012) [43] (n = 14,000 families) found a link between low birth weight in offspring and an increased cardiovascular risk among fathers, as well as a relation between low offspring birth weight and unfavorable glucose levels, increased blood pressure and high BMI values among fathers [43]. Hillman et al. (2013) [44] showed that fathers of offspring with a fetal growth-restriction were more likely to be insulin resistant, hypertensive and obese compared to fathers of normal grown offspring [44]. Furthermore, Moss et al. (2015) [45], Hyppönen et al. (2003) [46] and Veena et al. (2006) [47], showed that paternal diabetes was obviously associated with low offspring birth weight. Lindsay at al. (2000) [48] determined that the development of paternal diabetes can be predicted by the offspring’s birth weight. Thereby, the highest diabetes risk was identified in fathers of children in the lowest quintile of birth weight. They found a distinct association between low birth weight and an elevated diabetes risk in the offspring itself. Lauenborg et al. (2011) [49] could demonstrate that adult offspring with low birth weight and diabetic fathers showed decreased insulin sensitivity as well as increased plasma glucose levels in the state of fasting and after oral glucose load [49].

Age. Advanced paternal age has been associated with a higher risk of spontaneous abortions, stillbirth, preterm birth as well as with congenital malformations, childhood cancer, epilepsy, autism and schizophrenia in offspring [50]. Zhu et al. (2008) identified a U-shaped association between paternal age and mortality rates of children [50]. Urhoj et al. (2014) [51] reported that the risk of an under-five mortality increased significantly if the father was older than 40 years at the time of child birth by increased likelihood of dying from congenital malformations or malignancies [51]. In addition, Zhu (2005) [52] found that the prevalence of malformations of extremities and syndromes of multiple systems (e.g. Down’s syndrome) increased with advancing paternal age [52]. Although Su et al. (2015) [53] showed no overall association between the father’s age and heart defects in offspring, advanced paternal age could be linked to an elevated prevalence of patent ductus arteriosus in the offspring, which is a subtype of congenital heart defects [53]. Khandwala et al. (2018) [54] linked advanced paternal age to an increased risk of premature birth and a low offspring birth weight.

Smoking and environmental chemical exposure. Marchzylo et al. (2012) [55] were able to show that cigarette smoke induced differential microRNA expression in the spermatozoa of smokers (compared to non-smokers). These altered microRNAs mediate pathways were essential for sperm and embryo development [55].
Pembrey et al. (2006) [42] focused on cigarette-induced transgenerational effects on offspring growth. Thereby, the authors found out that there is a transgenerational effect of paternal mid-childhood smoking on offspring BMI at 9 years. However, this effect was only observed in boys (see Table 1). Based on their observation that exposure in the slow growth period can lead to a transgenerational effect, Pembrey et al. proved the existence of a sex-specific, male-line transgenerational response system in humans, which is presumably mediated by the gonosomes. Further, the authors assumed that this male transgenerational response is carried by the sperm’s chromosomes e.g. through viruses, prions, RNA molecules or responsive DNA sequences [42].

De Jonge et al. (2013) [56] reported that paternal smoking of 15 cigarettes per day or more was associated with an increased risk of hypertension in adult offspring. Further, Dior et al. (2014) [57] displayed a positive association between maternal and paternal smoking and offspring weight, height and BMI at the age of 17 and a negative association with pulse rates. Similar findings were found at the age of 32 if at least one parent was smoking [57].

Golding et al. (2019) [56] demonstrated that regular paternal cigarette smoking before the age of 11 was strongly associated with an elevated fat mass in adulthood of the respective children [58]. However, these findings do not agree with the study results of Carslake et al. (2016) [59] which found no clear association between paternal early-onset smoking (before the age of 11) and higher BMI values in offspring [59]. Instead, another study by Dougan et al. (2016) [60] could show that grand-paternal smoking during pregnancy of the grandmother was associated with a higher risk for granddaughters at the age of 12 to be overweight or obese. A link between grand-paternal smoking and the BMI of the grandson was not established [60]. Deng et al. (2013) [61] and Cresci et al. (2011) [62] reported that paternal smoking was associated with conotruncal heart defects.

Beside cigarette smoke, there are various other chemicals, which also represent transgenerational risk factors for offspring health. In this context frequently mentioned chemicals are persistent organic pollutants (e.g. dioxins or insecticides), which belong to the group of developmental toxicants [63, 64]. Robledo et al. (2015) [63] were able to show that birth size and weight of the offspring was affected by the pre-conceptional paternal exposure to persistent organic pollutants. In contrast, Lawson et al. (2004) [64] did not found an association between paternal exposure to dioxins and adverse pregnancy outcomes. Other studies, which focused on occupations of fathers that involve contact with toxic substances, also provide conflicting and no clear results regarding the effects on offspring health [65, 66].

**Paternal risk factors: Experimental studies**

**High-fat diet and obesity.** Ng et al. (2010) [24] investigated the effect of an induced high-fat-diet on F1 female offspring. They hypothesized that an intergenerational transmission of obesity and metabolic diseases can be initiated by the father through exposure to a high-fat-diet. The authors analyzed male rats (high-fat-diet or control diet) with females (control diet). The high-fat-diet fed male rats exhibited increased body weight, energy intake, adiposity, plasma leptin and liver mass, as well glucose intolerance and insulin resistance compared to rats on control diet, and their female litter showed adiposity and insulin resistance similar according their fathers [24]. Female progeny presented increased blood glucose, reduced insulin secretion as well as reduced β-cell and islet area [24] (see Table 1).

Masuyama et al. (2016) [67] demonstrated that offspring of high-fat diet fed male rats showed a metabolic syndrome-like phenomena, which includes weight and fat gain, glucose intolerance as well as elevated total triglyceride, decreased adiponectin, and increased leptin levels. This phenomena could be observed across two generations [67]. In addition, Ornellas
et al [68] showed an impaired glucose metabolism and lipogenesis (without an influence on beta-oxidation) and enhanced hepatic steatosis in male high-fat diet fed mice.

In accordance with Ng et al. (2014) [69], McPherson et al. (2015) [23] outlined that paternal obesity in mice, which was induced by a high-fat diet prior to conception, caused insulin resistance and increased the accumulation of adipose tissue in their female offspring. Short-term diet and exercise interventions in fathers improved the metabolic health of the female offspring [23] (see Table 1).

Fullston et al. (2013) [70] could demonstrate that paternal exposure to a high-fat diet in mice, which caused obesity, induced a specific transgenerational phenotypic constellation of impaired glucose tolerance, insulin resistance in both male and female offspring [70]. Another study by Fullston et al. (2015) showed that both paternal obesity at conception and a consumption of a high-fat diet by an individual animal caused the development of a metabolic syndrome and subfertility.

A growth deficit in mate rat offspring of high-fat diet fed fathers, which led to a body weight reduction of 10% at the age of six months and which resulted in smaller fat pads and less muscle mass was detected by Lecomte et al. (2017) [71]. Krout et al. (2018) [70] showed that paternal exercise before conception can reduce the offspring’s risk of developing T2DM, which was induced by the fathers high-fat diet, assuming epigenetic alterations in sperm DNA. Further, Consitt et al. (2018) noted that a pre-conceptional paternal high-fat diet enhances skeletal muscle insulin sensitivity as well as whole-body insulin sensitivity in the early life of the offspring [72]. Offspring of high-fat diet fed fathers were more susceptible to gain body fat in the early stage of adulthood [72]. Further, Fullston et al. [73] indicated a high fat diet-induced paternal initiation of subfertility in offspring of two generations of mice.

**Low protein diet.** In the study by Watkins and Sinclair (2014) [74], adult offspring of low protein diet-fed male mice developed a significantly impaired cardiovascular and metabolic homeostasis, vascular dysfunction, impaired glucose tolerance as well as elevated adiposity in adulthood [74].

Paternal low protein diet in mice especially affected the signaling pathways of the lipid metabolism according to Carone et al. (2010) [75]. A significant increase in the relative concentration of saturated cardiolipins, saturated free fatty acids and saturated and monounsaturated triacyl-glycerides was observed in the progeny [75].

**Undernutrition.** Referring to Anderson et al. (2006) [76], paternal food deprivation in male mice caused a consistent decrease in average serum glucose and changes in corticosterone and insulin-like growth factor 1 in both male and female offspring [76].

McPherson et al. (2016) [25] noted that undernutrition in mice led to dyslipidemia, accumulation of adipose tissue, an altered expression of pancreatic genes, and reduced weight in male and female offspring [25] (see Table 1). In addition, vitamin and antioxidant supplements given to undernourished fathers normalized offspring weight and growth [25].

**Hyperglycemia.** Grasemann et al. (2012) [77] indicated in mice, that metabolic parameters were affected more by maternal than paternal hyperglycemia, and the skeletal development (changes in bone mineral content, trabecular structure, and cortical bone properties) was more affected by paternal hyperglycemia [77]. According to Shi et al. (2017) [78], the adult offspring of hyperglycemic male rats showed a significant weight gain, larger body size and an extensive expansion of adipose tissue resulting in obesity of the offspring. Glucose intolerance, reduced insulin sensitivity and impaired hypothalamic leptin signaling was identified in male offspring [78]. Similar conclusions were drawn by Li et al. (2019) [79] showing an increased liver weight, elevated plasma total cholesterol, triglyceride as well LDL levels as an accumulation of triglycerides in the liver in adult rat offspring of hyperglycemic fathers. Furthermore,
the authors detected epigenetic alterations affecting the PPAR-alpha promoter in the liver of
the offspring [79].

Wei et al. (2014) [80] determined that paternal prediabetes affected the overall methylation
patterns in pancreatic islets of offspring and in sperm of the father [80].

**Environmental chemical exposures.** Lane et al. (2014) [81] observed in mice that an
increased level of reactive oxygen species (ROS) in sperm and/or seminal fluid influences off-
spring health outcome in a negative way by poorer embryo development and reduced fetal
growth. The ROS concentration was significantly increased in relation to cancer, smoking,
obesity, chemical exposure and ageing [81]. Daughters from exposed fathers were smaller,
developed a glucose intolerance and exhibited an increased adipose tissue accumulation [81].
Referring to McPherson et al. (2016), ROS mediated sperm DNA lesions could be reduced by
vitamin and antioxidant supplementation, which increased the sperm health and correlated
negatively with the postnatal growth of the male offspring [25].

Genotoxic agent benzo[a]pyrene (B[a]P) is a component of diesel emissions, tobacco
smoke and smoked food products [82]. Godschalk et al. (2018) [82] observed a down-regula-
tion of mitochondrial proteins in offspring of B[a]P exposed mice, and specially in male off-
spring an additional reduction of mitochondrial DNA copies could be identified [82].

### Discussion

#### Principal findings

This systematic scoping review identified possible paternal risk factors affecting trans-genera-
tional cardio-metabolic programming such as obesity, birth weight, high-fat and low-protein
diet, undernutrition, diabetes mellitus, hyperglycaemia, advanced age, smoking as well as envi-
ronmental chemical exposure (Fig 2).

As one of the most common adverse life style factors, paternal obesity could be pointed out
as initiator of changes in sperm epigenetics, such as alterations in sperm DNA methylation
and acetylation patterns [73]. Paternal obesity can lead to metabolic disturbances and changes
in the transcriptome of genes in pathways regulating cellular response to stress, cell death and
cell growth in adipose tissue of consecutive generations [23]. Further, male pre-conceptional
obesity is able to reduce fetal growth, causes cardiovascular diseases and might be responsible
for alterations in the glucose metabolism of the offspring. Also, an increased risk of developing
obesity and insulin resistance in the offspring’s later life is associated with a high paternal BMI
[16, 22, 27, 28]. Metabolic impairments in offspring are often associated with the paternal diet
(high fat or low protein) and his nutrition status. For example, a high-fat diet of fathers in the
time of conception is related to an impaired glucose metabolism, insulin resistance, weight
gain, elevated triglyceride and increased leptin levels in the following generation [24, 67, 68]. A
diet based on foods with low protein can also lead to an impairment of the cardiovascular and
metabolic homeostasis [74]. In addition, the nutrition status of the father plays an important
role in the context of metabolic offspring health. So, a prenatal exposure to a famine might
increase the offspring’s risk of developing diabetes in later life [36]. In conclusion, obesity and
the nutrition status of the father might play an important role in the context of metabolic off-
spring health [36].

Paternal diabetes was associated with a higher probability of developing diabetes in off-
spring [39]. Furthermore, children with diabetic fathers displayed an impaired insulin sensitiv-
ity and higher BMI values than children of non-diabetic fathers [40, 41]. In addition, advanced
paternal age has been shown to induce DNA damage and de novo mutations. These factors
entail considerable health risks for the offspring of aged fathers, e.g. low birthweight, preterm
birth, congenital malformations, mental disorders or an increased overall mortality risk under the age of five [50–53].

Furthermore, smoking induces alterations in spermatozoa microRNA which are essential for sperm and embryo development [55]. Tobacco smoke initiates cardiovascular diseases, cancer, chronic lung diseases and increases the risk of adult-onset hypertension and overweight in offspring [56, 58, 61, 83]. In addition, the indirect harm done by maternal passive smoking has to be taken into account [83]. At last, the results of paternal exposure to different chemicals, which may trigger DNA mutations through increased ROS level in sperm, have been summarized. Amongst others, the exposure of paternal sperm to toxic chemicals led to poorer embryo development and reduced fetal growth [63, 81]. Further, negative alterations in the mitochondrial metabolism could be detected [82].
Our findings are in line with other reviews. Bodden et al. (2019) [84] reported that paternal obesity as a result of an excessive consumption of high calorie foods, leading to metabolic and neurobiological changes, can predict adverse offspring health outcomes. In addition, Sharp and Lawlor (2019) [85] linked paternal factors (e.g. paternal age, environmental exposures, high-fat-diet-induced obesity) to offspring development of obesity and type 2 diabetes. Likewise, Li et al. (2016) [86] indicated that paternal under and overnutrition, environmental toxin exposure, paternal diabetes, and grandfather’s nutritional status can program cardio-metabolic diseases in offspring via germ cell-mediated transmission. Further, Campbell and Mcpherson (2019) [87] found that increased paternal BMI clearly affected pregnancy and offspring health outcome, for example leading to an increased BMI in childhood.

Furthermore, epigenetic mechanisms linking paternal well-being to offspring health have been analyzed. Watkins et al. [88] highlighted the role of the seminal plasma for offspring programming independent from that of the sperm. Chen et al. (2016) [89] indicated that tsRNA isolated from sperm from obese male mice recapitulates the paternal programming of offspring ill-health when compared to interact sperm. Lambrot et al. (2013) [90] found that epigenetic transmission may contain sperm histone H3 methylation or DNA methylation. Adequate paternal dietary folate is substantial for offspring health. In addition, according to Chan et al. (2020) [91], extracellular vesicles as a normal process in sperm maturation can perform roles in intergenerational transmission of paternal environmental experience.

Furthermore, limitations might have an impact on our findings. To the best of our knowledge and considering our inclusion and exclusion criteria, we involved all eligible studies. The publications were heterogeneous regarding study population, and evidence on some individual risk factors is limited. In some sections, such as the risk factor nutrition, we could only identify a few studies.

Maternal vs. paternal programming. The transmission of parental phenotypes to the offspring can be influenced by different environmental factors that induce epigenetic changes in oocytes and sperm [80, 92]. Epigenetic changes include variations in levels of DNA methylation, histone modification and the regulation of non-coding RNAs [23, 80]. Male individuals can affect offspring health through the quality of their sperm [80]. In case of female individuals, different environmental and lifestyle factors can shift epigenetic conditions leading to an adverse intrauterine environment. Lifestyle factors affect epigenetic modifications in genes of oocytes and decrease the oocytes’ quality. Alterations of the maternal intrauterine environment and reduction of the quality of oocytes may result in impaired fetal growth or developmental defects [93, 94].

A high maternal pre-conceptional BMI is known to be an important risk factor for adiposity, insulin resistance, impaired glucose tolerance and cardio-metabolic disease risk in the offspring [95, 96]. Other than maternal obesity, the father’s obesity seems to greatly affect the amount and distribution of bodyfat as well as adipokine levels in offspring of the next two generations [20, 27, 28]. Especially female offspring showed an impaired glucose-insulin homeostasis, which was transmitted via paternal lineage [23]. In male offspring, paternal obesity was associated with decreased fertility [73].

Both maternal and paternal diet high in fat and sugar seem to lead to impaired glucose and insulin metabolism, higher risk developing T2DM, adiposity, hypertension and hepatic disease in the offspring’s later life [67, 97].

Maternal diabetes was strongly associated with an increased birth weight and elevated diabetes risk in the offspring [47] and maternal transmission of T2DM is threefold higher than paternal transmission [98]. Paternal diabetes was clearly linked to low birth weight in the offspring, lower gestational age [47], influencing glucose and insulin levels, and increased risk of T2DM in adulthood [80].
In utero exposure to maternal smoking was linked to obesity, T2DM and cardiovascular diseases in adult offspring [57]. In comparison with maternal smoking, pre-conceptional paternal smoking as well as paternal smoking during pregnancy were associated with an increased risk of congenital malformations and heart defects in the offspring [61, 62]. Studies also showed an association between paternal smoking and an elevated risk of hypertension in later offspring life as well as increased BMI [21].

Furthermore, advanced maternal age was linked to an elevated risk of pregnancy complications, preterm birth and cardiovascular diseases in adult offspring [99]. Velazquez et al. (2016) could demonstrate that offspring from aged mice was prone to hypertension and showed higher weight gain in post-natal life than offspring of young female mice [100]. One explanation for these adverse pregnancy outcomes might be a decreased egg quality and an altered uterine environment of the mother [101]. In comparison with maternal age, there was also an obvious association between aged fathers and an increased risk for stillbirth, preterm birth, congenital malformations and offspring death [50, 51, 53, 54].

In general, comparable to maternal programming, paternal factors also have a substantial effect on trans-generational programming leading to adverse metabolic and cardiovascular outcomes in their offspring.

Conclusions

In total, the evidence from several epidemiological, clinical, and experimental human and animal model studies indicates that paternal risk factors such as obesity, high-fat and low-protein diet, undernutrition, diabetes mellitus, hyperglycemia, advanced age, smoking as well as environmental chemical exposure might affect offspring health leading to adverse metabolic and cardiovascular outcomes (Fig 2). Comparable to maternal programming, pre-conceptional paternal factors might also have a substantial “programming” effect. Additional research on paternal risk factors, the underlying physiological mechanism of paternal programming, and the trans-generational inheritance is needed.

Considering our findings, an appropriate pre-conception care including medical, behavioural and social health interventions is very important to reduce the risk of epigenetic disorders and negative environmental exposures in order to improve offspring health as well as the parental health status [102]. Preventive and educational approaches clearly include both, mothers and fathers (to be), to reduce adverse health outcomes in their offspring caused by modifiable lifestyle and environmental risk factors effectively.

Supporting information

S1 Checklist. PRISMA checklist.
(DOC)

S1 File.
(DOCX)

S2 File.
(DOCX)

Author Contributions

Conceptualization: Claudia Eberle, Stefanie Stichling.

Data curation: Claudia Eberle, Michaela F. Kirchner, Raphaela Herden, Stefanie Stichling.
Formal analysis: Claudia Eberle.
Investigation: Claudia Eberle.
Methodology: Claudia Eberle, Stefanie Stichling.
Project administration: Claudia Eberle.
Resources: Claudia Eberle.
Software: Claudia Eberle.
Supervision: Claudia Eberle.
Validation: Claudia Eberle.
Visualization: Claudia Eberle.
Writing – original draft: Claudia Eberle, Michaela F. Kirchner, Raphaela Herden, Stefanie Stichling.
Writing – review & editing: Claudia Eberle, Stefanie Stichling.

References
1. Eberle C, Ament C. Diabetic and Metabolic Programming: Mechanisms Altering the Intrauterine Milieu. ISRN Pediatrics. 2012; 2012:1–11. https://doi.org/10.5402/2012/975685 PMID: 23213562
2. Eberle C. Fetale Programmierung des Diabetes mellitus Typ 2. MMW-Fortschritte der Medizin Originalien. 2010; 152:S. 76–82.
3. Eberle C, Merki E, Yamashita T, Johnson S, Armando AM, Quehenberger O, et al. Maternal immunization affects in utero programming of insulin resistance and type 2 diabetes. PLoS ONE. 2012; 7: e45361. https://doi.org/10.1371/journal.pone.0045361 PMID: 23028961.
4. Yamashita T, Freigang S, Eberle C, Pattison J, Gupta S, Napoli C, et al. Maternal immunization programs postnatal immune responses and reduces atherosclerosis in offspring. Circ Res. 2006; 99: e51–64. https://doi.org/10.1161/01.RES.0000244003.08127.cc PMID: 16946133.
5. Eberle C, Ament C. A combined in vivo and in silico model shows specific predictors of individual trans-generational diabetic programming. J Dev Orig Health Dis. 2020:1–8. https://doi.org/10.1017/S2040174420000471 PMID: 32808917.
6. Eberle C, Stupin JH. 6.5 Perinatale Programmierung. In: Stupin JH, Schäfer-Graf U, Hummel M, editors. Diabetes in der Schwangerschaft. De Gruyter; 2020. pp. 242–65.
7. Hales CN, Barker DJP. The thrifty phenotype hypothesis. British Medical Bulletin. 2001; 60:5–20. https://doi.org/10.1093/bmb/60.1.5 PMID: 11809615
8. Wells JC. Commentary: Paternal and maternal influences on offspring phenotype: the same, only different. International Journal of Epidemiology. 2014; 43:772–4. https://doi.org/10.1093/ije/dyu055 PMID: 24651398
9. Hocher B. More than genes: the advanced fetal programming hypothesis. Journal of Reproductive Immunology. 2014; 104–105:8–11. https://doi.org/10.1016/j.jri.2014.03.001 PMID: 24721253
10. Eberle C, Kirchner M. Paternale Programmierung: Präkonzeptionelle Risikofaktoren in Bezug auf das Diabetes-Risiko der Nachkommen. Diabetes –Nicht nur eine Typ-Frage– www.diabeteskongress.de. Georg Thieme Verlag KG; 2019.
11. Herden R, Eberle C. Paternale Einflussfaktoren auf das Diabetes-Risiko der Nachkommen. Diabetes und Stoffwechsel. 2018; 13. https://doi.org/10.1055/s-0038-1641924
12. Hur SSJ, Croyple JE, Suter CM. Paternal epigenetic programming: evolving metabolic disease risk. Journal of molecular endocrinology. 2017; 58:R159–R168. https://doi.org/10.1530/JME-16-0236 PMID: 28100703.
13. Peters MDJ, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015; 13:141–6. https://doi.org/10.1097/XEB.0000000000000050 PMID: 26134548.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6:e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072.
15. Labayen I, Ruiz JR, Ortega FB, Loit HM, Harro J, Veidebaum T, et al. Intergenerational Cardiovascular Disease Risk Factors Involve Both Maternal and Paternal BMI. Diabetes Care. 2010; 33:894–900. https://doi.org/10.2337/dc09-1878 PMID: 20056951

16. Santos Ferreira DL, Williams DM, Kangas AJ, Soininen P, Ala-Korpela M, Smith GD, et al. Association of pre-pregnancy body mass index with offspring metabolic profile: Analyses of 3 European prospective birth cohorts. PLoS Med. 2017; 14:e1002376. https://doi.org/10.1371/journal*pmed.1002376 PMID: 28829768

17. McCarthy K, Ye Y-I, Yuan S, He Q-q. Parental Weight Status and Offspring Cardiovascular Disease Risks: a Cross-Sectional Study of Chinese Children. Prev Chronic Dis. 2015; 12. https://doi.org/10.5888/pcd12.140384 PMID: 25569694

18. Gaillard R, Steegers EAP, Duijts L, Felix JF, Hofman A, Franco OH, et al. Childhood Cardiometabolic Outcomes of Maternal Obesity During Pregnancy. Hypertension. 2014; 63:683–91. https://doi.org/10.1161/HYPERTENSIONAHA.113.02671 PMID: 24379180

19. Zaalbahr N, Najman J, McIntyre HD, Mamun A. Parental pre-pregnancy BMI influences on offspring BMI and waist circumference at 21 years. Australian and New Zealand Journal of Public Health. 2016; 40:572–8. https://doi.org/10.1111/1753-6405.12574 PMID: 27624991

20. Sørensen TIA, Ajslev TA, Ångquist L, Morgen CS, Ciuchi IG, Davey Smith G. Comparison of associations of maternal peri-pregnancy and paternal anthropometrics with child anthropometrics from birth through age 7 y assessed in the Danish National Birth Cohort. Am J Clin Nutr. 2016; 104:389–96. https://doi.org/10.3945/ajcn.115.129171 PMID: 27413126

21. Pembrey ME, Bygren LO, Kaati G, Edvinsson S, Northstone K, Sjöström M, et al. Sex-specific, male-line transgenerational responses in humans. Eur J Hum Genet. 2006; 14:159–66. https://doi.org/10.1038/sj.ejhg.5201538 PMID: 16391557

22. Chen Y-P, Xiao X-M, Li J, Reichetzer C, Wang Z-N, Hocher B. Paternal body mass index (BMI) is associated with offspring intrauterine growth in a gender dependent manner. PLoS ONE. 2012; 7:e36329. https://doi.org/10.1371/journal.pone.0036329 PMID: 22570703

23. McPherson NO, Owens JA, Fullston T, Lane M. Preconception diet or exercise intervention in obese fathers normalizes sperm microRNA profile and metabolic syndrome in female offspring. American Journal of Physiology-Endocrinology and Metabolism. 2015; 308:E158–E165. https://doi.org/10.1152/ajpendo.00013.2015 PMID: 25690453

24. Ng S-F, Lin RCY, Laybutt DR, Barres R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs β-cell dysfunction in female rat offspring. Nature. 2010; 467:963–6. https://doi.org/10.1038/nature09491 PMID: 20962845

25. McPherson NO, Fullston T, Kang WX, Sandeman LY, Corbett MA, Owens JA, et al. Paternal under-nutrition programs metabolic syndrome in offspring which can be reversed by antioxidant/vitamin food fortification in fathers. Sci Rep. 2018; 8. https://doi.org/10.1038/s41598-018-0015-2 PMID: 28442741

26. Almari M, Alsaeedi S, Mohammad A, Ziyab AH. Associations of adiposity and parental diabetes with prediabetes among adolescents in Kuwait: A cross-sectional study. Pediatri Diabetes. 2018; 19:1362–9. https://doi.org/10.1111/pedi.12780 PMID: 30255624

27. Gaillard R, Steegers EAP, Duijts L, Felix JF, Hofman A, Franco OH, et al. Childhood cardiometabolic outcomes of maternal obesity during pregnancy: the Generation R Study. Hypertension. 2014; 63:683–91. https://doi.org/10.1161/HYPERTENSIONAHA.113.02671 PMID: 24379180

28. McCarthy K, Ye Y-I, Yuan S, He Q-q. Parental weight status and offspring cardiovascular disease risks: a cross-sectional study of Chinese children. Prev Chronic Dis. 2015; 12:E01. https://doi.org/10.5888/pcd12.140384 PMID: 25569694.

29. Labayen I, Ruiz JR, Ortega FB, Loit HM, Harro J, Veidebaum T, et al. Intergenerational cardiovascular disease risk factors involve both maternal and paternal BMI. Diabetes Care. 2010; 33:894–900. https://doi.org/10.2337/dc09-1878 PMID: 20056951

30. Magnus MC, Olsen SF, Granstrom C, Lund-Blax NIA, Svensson J, Johannessen J, et al. Paternal and maternal obesity but not gestational weight gain is associated with type 1 diabetes. International Journal of Epidemiology. 2018; 47:417–26. https://doi.org/10.1093/ije/dyx266 PMID: 29415279

31. Veena SR, Krishnaveni GV, Karat SC, Osmond C, Fall CHD. Testing the fetal overnutrition hypothesis: the relationship of maternal and paternal adiposity to adiposity, insulin resistance and cardiovascular risk factors in Indian children. Public Health Nutr. 2013; 16:1656–66. https://doi.org/10.1017/S1368980012003795 PMID: 22895107

32. Soubry A, Schildkraut JM, Murtha A, Wang F, Huang Z, Bernal A, et al. Paternal obesity is associated with IGF2 hypomethylation in newborns: results from a Newborn Epigenetics Study (NEST) cohort. BMC Med. 2013; 11:29. https://doi.org/10.1186/1741-7015-11-29 PMID: 23388414.
33. McCowan LME, North RA, Kho EM, Black MA, Chan EHY, Dekker GA, et al. Paternal contribution to small for gestational age babies: a multicenter prospective study. Obesity (Silver Spring). 2011; 19:1035–9. https://doi.org/10.1038/oby.2010.279 PMID: 21127471.

34. Derraik JGB, Pasupathy D, McCowan LME, Poston L, Taylor RS, Simpson NAB, et al. Paternal contributions to large-for-gestational-age term babies: findings from a multicenter prospective cohort study. J Dev Orig Health Dis. 2019; 10:529–35. https://doi.org/10.1017/S2040174419000035 PMID: 30813979.

35. Kaati G, Lo Bygren, Edvinsson S. Cardiovascular and diabetes mortality determined by nutrition during parents’ and grandparents’ slow growth period. Eur J Hum Genet. 2002; 10:682–8. https://doi.org/10.1046/j.1365-2141.2002.01303.x PMID: 12404098.

36. Li J, Liu S, Li S, Feng R, Na L, Chu X, et al. Prenatal exposure to famine and the development of hyperglycemia and type 2 diabetes in adulthood across consecutive generations: a population-based cohort study of families in Suihua, China. Am J Clin Nutr. 2017; 105:221–7. https://doi.org/10.3945/ajcn.116.138792 PMID: 27927634.

37. Penesova A, Bunt JC, Bogardus C, Krakoff J. Effect of paternal diabetes on pre-diabetic phenotypes in adult offspring. Diabetes Care. 2010; 33:1823–8. https://doi.org/10.2337/dc09-2044 PMID: 20519666.

38. Silva DR, Werneck AO, Collings PJ, Fernandes RA, Barbosa DS, Ronque ERV, et al. Family history of cardiovascular disease and parental lifestyle behaviors are associated with offspring cardiovascular disease risk markers in childhood. Am J Hum Biol. 2017; 29:e22995. https://doi.org/10.1002/ajhb.22995 PMID: 28295804.

39. Wang C, Yatsuya H, Tamakoshi K, Toyoshima H, Wada K, Li Y, et al. Association between parental diabetes and birth weight of offspring: intergenerational cohort study. BMJ. 2017; 357:j2728. https://doi.org/10.1136/bmj.j2728 PMID: 28287371.

40. Ammini A, Dwivedi S, Gupta N, Khadgawat R, Khurana M, Kulshreshtha B, et al. Insulin sensitivity and β-cell function in normoglycemic offspring of individuals with type 2 diabetes mellitus: Impact of line of inheritance. Indian J Endocr Metab. 2012; 16:105. https://doi.org/10.4103/2227-2337.98100 PMID: 22762620.

41. Linares Segovia B, Gutiérrez Tinoco M, Izquierdo Arrizón A, Guizar Mendoza JM, Amador Licona N. Long-term consequences for offspring of paternal diabetes and metabolic syndrome. Exp Diabetes Res. 2012; 2012:684562. https://doi.org/10.1155/2012/684562 PMID: 23193389.

42. Shields BM, Knight B, Turner M, Wilkins-Wall B, Shakespeare L, Powell RJ, et al. Paternal insulin resistance and its association with umbilical cord insulin concentrations. Diabetologia. 2006; 49:2684–74. https://doi.org/10.1007/s00125-006-0282-8 PMID: 16703330.

43. Myklestad K, Vatten LJ, Magnussen EB, Salvesen KÅ, Smith GD, Romundstad PR. Offspring birth weight and cardiovascular risk in parents: a population-based HUNT 2 study. Am J Epidemiol. 2012; 175:546–55. https://doi.org/10.1093/aje/kwr347 PMID: 22328703.

44. Hillman S, Peebles DM, Williams DJ. Paternal metabolic and cardiovascular risk factors for fetal growth restriction: a case-control study. Diabetes Care. 2013; 36:1675–80. https://doi.org/10.2337/dc12-1280 PMID: 23315598.

45. Moss JL, Harris KM. Impact of maternal and paternal preconception health on birth outcomes using prospective couples’ data in Add Health. Arch Gynecol Obstet. 2015; 291:287–98. https://doi.org/10.1007/s00404-014-3521-0 PMID: 25367598.

46. Hypponen E. Parental diabetes and birth weight of offspring: intergenerational cohort study. BMJ. 2003; 326:19–20. https://doi.org/10.1136/bmj.326.7379.19 PMID: 12511454.

47. Veena SR, Geetha S, Leamy SD, Saperia J, Fisher DJ, Kumaran K, et al. Relationships of maternal and paternal birthweights to features of the metabolic syndrome in adult offspring: an inter-generational study in South India. Diabetologia. 2006; 50:43–54. https://doi.org/10.1007/s00125-006-0516-9 PMID: 17143606.

48. Lindsay RS, Dabelea D, Roumian J, Hanson RL, Bennett PH, Knowler WC. Type 2 diabetes and low birth weight: the role of paternal inheritance in the association of low birth weight and diabetes. Diabetologia. 2000; 43:445–9. https://doi.org/10.2337/diabetes.43.3.445 PMID: 10868967.

49. LAUENBORG J, JØRGENSEN MKE, DANNM P, MAJOR-PEDERSEN A, EIBLE H, URHAMMER S, et al. The influence of parental history of diabetes and offspring birthweight on offspring glucose metabolism in adulthood. Acta Obstetrica et Gynecologica Scandinavica. 2011; 90:1357–63. https://doi.org/10.1111/j.1600-0412.2011.01276.x PMID: 21916855.

50. Zhu JL, Vestergaard M, Madsen KM, Olsen J. Paternal age and mortality in children. Eur J Epidemiol. 2008; 23:443–7. https://doi.org/10.1007/s10654-008-9253-3 PMID: 18437509.
51. Urhoj SK, Jespersen LN, Nissen M, Mortensen LH, Nybo Andersen A-M. Advanced paternal age and mortality of offspring under 5 years of age: a register-based cohort study. Human Reproduction. 2014; 29:343–50. https://doi.org/10.1093/humrep/det399 PMID: 24316515

52. Zhu JL, Madsen KM, Vestergaard M, Olesen AV, Basso O, Olsen J. Paternal age and congenital malformations. Human Reproduction. 2005; 20:3173–7. https://doi.org/10.1093/humrep/dei186 PMID: 16006461

53. Su JK, Yuan W, Huang GY, Olsen J, Li J. Paternal Age and Offspring Congenital Heart Defects: A National Cohort Study. PLoS ONE. 2015; 10:e0121030. https://doi.org/10.1371/journal.pone.0121030 PMID: 25806788

54. Khandwala YS, Baker VL, Shaw GM, Stevenson DK, Lu Y, Eisenberg ML. Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study. BMJ. 2018:k4372. https://doi.org/10.1136/bmj.k4372 PMID: 30381468

55. Marczylo EL, Amoako AA, Konje JC, Gant TW, Marczylo TH. Smoking induces differential miRNA expression in human spermatozoa: a potential transgenerational epigenetic concern. Epigenetics. 2012; 7:432–9. https://doi.org/10.4161/epi.19794 PMID: 22441141.

56. Jonge LL de, Harris HR, Rich-Edwards JW, Willett WC, Forman MR, Jaddoe VWV, et al. Parental smoking during pregnancy and the risks of adult-onset hypertension. Hypertension. 2013; 61:494–500. https://doi.org/10.1161/HYPERTENSIONAHA.112.200907 PMID: 23266542.

57. Dior UP, Lawrence GM, Sittiani C, Enquobahrie D, Manor O, Siscovick DS, et al. Parental smoking during pregnancy and offspring cardio-metabolic risk factors at ages 17 and 32. Atherosclerosis. 2014; 235:430–7. https://doi.org/10.1016/j.atherosclerosis.2014.05.937 PMID: 24937467

58. Golding J, Gregory S, Northstone K, Iles-Caven Y, Ellis G, Pembrey M. Investigating Possible Trans/Intergenerational Associations With Obesity in Young Adults Using an Exposome Approach. Front Genet. 2019; 10. https://doi.org/10.3389/fgen.2019.00010 PMID: 30815010

59. Carslake D, Pinger PR, Romundstad P, Davey Smith G, Fowles ET. Early-Onset Paternal Smoking and Offspring Adiposity: Further Investigation of a Potential Intergenerational Effect Using the HUNT Study. PLoS ONE. 2016; 11:e0166952. https://doi.org/10.1371/journal.pone.0166952 PMID: 27911909

60. Dougan MM, Field AE, Rich-Edwards JW, Hankinson SE, Glynn RJ, Willett WC, et al. Is grand-parental smoking associated with adolescent obesity? A three-generational study. Int J Obes. 2016; 40:531–7. https://doi.org/10.1038/ijo.2015.186 PMID: 26388349

61. Deng K, Liu Z, Lin Y, Mu D, Chen X, Li J, et al. Periconceptional paternal smoking and the risk of congenital heart defects: A case-control study. Birth Defects Research Part A: Clinical and Molecular Teratology. 2013; 97:210–6. https://doi.org/10.1002/bdra.23128 PMID: 23554276

62. Cresci M, Foffa I, Ait-Ali L, Pulignani S, Gianicolo EAL, Botto N, et al. Maternal and Paternal Environmental Risk Factors, Metabolizing GSTM1 and GSTT1 Polymorphisms, and Congenital Heart Disease. The American Journal of Cardiology. 2011; 108:1625–31. https://doi.org/10.1016/j.amjcard.2011.07.022 PMID: 21890078

63. Robledo CA, Yeung E, Mendola P, Sundaram R, Maisog J, Sweeney AM, et al. Preconception Maternal and Paternal Exposure to Persistent Organic Pollutants and Parental Smoking: The LIFE Study. Environmental Health Perspectives. 2015; 123:88–94. https://doi.org/10.1289/ehp.1308016 PMID: 25095280

64. Lawson CC, Schnorr TM, Whelan EA, Deddens JA, Dankovic DA, Piacitelli LA, et al. Paternal Occupational Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Birth Outcomes of Offspring: Birth Weight, Preterm Delivery, and Birth Defects. Environmental Health Perspectives. 2004; 112:1403–8. https://doi.org/10.1289/ehp.7051 PMID: 15471733.

65. Magnusson LL, Bodin L, Wennborg H. Adverse pregnancy outcomes in offspring of fathers working in biomedicine research laboratories. Am J Ind Med. 2006; 49:468–73. https://doi.org/10.1002/ajim.20317 PMID: 16691607

66. Desrosiers TA, Herring AH, Shapira SK, Hooiveld M, Luben TJ, Herdt-Losavio ML, et al. Paternal occupation and birth defects: findings from the National Birth Defects Prevention Study. Occup Environ Med. 2012; 69:534–42. https://doi.org/10.1136/oemed-2011-100372 PMID: 22782864

67. Masuyama H, Mitsui T, Eguchi T, Tamada S, Hiramatsu Y. The effects of paternal high-fat diet exposure on offspring metabolism with epigenetic changes in the mouse adiponecint and leptin gene promoters. American Journal of Physiology-Endocrinology and Metabolism. 2016; 311:E236–E245. https://doi.org/10.1152/ajpendo.00055.2016 PMID: 27245335

68. Omellas S, Souza-Mello V, Mandarim-de-Lacerda CA, Aguiar MB. Programming of obesity and comorbidities in the progeny: lessons from a model of diet-induced obese parents. PLoS ONE. 2015; 10:e0124737. https://doi.org/10.1371/journal.pone.0124737 PMID: 25880318.

69. Ng S-F, Lin RCY, Maloney CA, Youngson NA, Owens JA, Morris MJ. Paternal high-fat diet consumption induces common changes in the transcriptomes of retroperitoneal adipose and pancreatic islet
tissues in female rat offspring. FASEB J. 2014; 28:1830–41. https://doi.org/10.1096/fj.13-244046 PMID: 24421403.

70. Fullston T, Ohlsson Teague EMC, Palmer NO, DeBlasio MJ, Mitchell M, Corbett M, et al. Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content. FASEB J. 2013; 27:4226–43. https://doi.org/10.1096/fj.12-224048 PMID: 23845863.

71. Lecomte V, Maloney CA, Wang KW, Morris MJ. Effects of paternal obesity on growth and adiposity of male rat offspring. American Journal of Physiology-Endocrinology and Metabolism. 2017; 312:E117–E125. https://doi.org/10.1152/ajpendo.00262.2016 PMID: 27965204.

72. Consitt LA, Saxena G, Slyvka Y, Clark BC, Friedlander M, Zhang Y, et al. Paternally induced transgenerational inheritance of susceptibility to hepatic steatosis in rats involving altered methylation on Ppar α promoter. Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease. 2019; 1865:147–60. https://doi.org/10.1016/j.bbadis.2018.10.040 PMID: 30404040.

73. Watkins AJ, Sinclair KD. Paternal low protein diet affects adult offspring cardiovascular and metabolic function in mice. American Journal of Physiology-Heart and Circulatory Physiology. 2014; 306:H1444–H1452. https://doi.org/10.1152/ajpheart.00981.2013 PMID: 24658019.

74. Carone BR, Faquier L, Habib N, Shea JM, Hart CE, Li R, et al. Paternally induced transgenerational environmental reprogramming of metabolic gene expression in mammals. Cell. 2010; 143:1084–96. https://doi.org/10.1016/j.cell.2010.12.008 PMID: 21183072.

75. Anderson LM, Riffle L, Wilson R, Travlos GS, Lubomirski MS, Alvord WG. Preconceptional fasting of fathers alters serum glucose in offspring of mice. Human Reproduction. 2012; 27:1391–400. https://doi.org/10.1093/humrep/des030 PMID: 22357767.

76. Sharp GC, Lawlor DA. Paternal impact on the life course development of obesity and type 2 diabetes in the offspring. Diabetologia. 2019; 62:1802–10. https://doi.org/10.1007/s00125-019-4919-9 PMID: 31451867.

77. Li J, Tsuprykov O, Yang X, Hocher B. Paternal programming of offspring cardiometabolic diseases in later life. J Hypertens. 2016; 34:2111–26. https://doi.org/10.1097/HJH.0000000000000105 PMID: 27457668.

78. Campbell JM, McPherson NO. Influence of increased paternal BMI on pregnancy and child health outcomes independent of maternal effects: A systematic review and meta-analysis. Obes Res Clin Pract. 2019; 13:511–21. https://doi.org/10.1016/j.orec.2019.11.003 PMID: 31767240.
88. Watkins AJ, Dias I, Tsuro H, Allen D, Ernes RD, Moreton J, et al. Paternal diet programs offspring health through sperm- and seminal plasma-specific pathways in mice. Proc Natl Acad Sci USA. 2018; 115:10064–9. https://doi.org/10.1073/pnas.1806333115 PMID: 30150380.

89. Chen Q, Yan M, Cao Z, Li X, Zhang Y, Shi J, et al. Sperm tRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. Science. 2016; 351:397–400. https://doi.org/10.1126/science.aad7977 PMID: 26721680.

90. Lambrot R, Xu C, Saint-Phar S, Chountalos G, Cohen T, Paquet M, et al. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. Nat Commun. 2013; 4:2889. https://doi.org/10.1038/ncomms2889 PMID: 24326934.

91. Chan JC, Morgan CP, Adrian Leu N, Shetty A, Cisse YM, Nugent BM, et al. Reproductive tract extracellular vesicles are sufficient to transmit intergenerational stress and program neurodevelopment. Nat Commun. 2020; 11:14499. https://doi.org/10.1038/s41467-020-15305-w PMID: 32198406.

92. Colton SA, Pieper GM, Downs SM. Altered meiotic regulation in oocytes from diabetic mice. Biol Reprod. 2002; 67:220–31. https://doi.org/10.1095/biolreprod67.1.220 PMID: 12080021.

93. Hou Y-J, Zhu C-C, Duan X, Liu H-L, Wang Q, Sun S-C. Both diet and gene mutation induced obesity affect oocyte quality in mice. Sci Rep. 2016; 6: https://doi.org/10.1038/srep18858 PMID: 26732298.

94. Ge Z-J, Luo S-M, Lin F, Liang Q-X, Huang L, Wei Y-C, et al. DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet-induced obesity. Environmental Health Perspectives. 2014; 122:159–64. https://doi.org/10.1289/ehp.1307047 PMID: 24316659.

95. Tan HC, Roberts J, Catov J, Krishnamurthy R, Shypailo R, Bacha F. Mother’s pre-pregnancy BMI is an important determinant of adverse cardiometabolic risk in childhood. Pediatr Diabetes. 2015; 16:419–26. https://doi.org/10.1111/pedi.12273 PMID: 25800542.

96. Dunn GA, Bale TL. Maternal high-fat diet effects on third-generation female body size via the paternal lineage. Endocrinology. 2011; 152:2228–36. https://doi.org/10.1210/en.2010-1461 PMID: 21447631.

97. Krout D, Roemmich JN, Bundy A, Garcia RA, Yan L, Claycombe-Larson KJ. Paternal exercise protects mouse offspring from high-fat-diet-induced type 2 diabetes risk by increasing skeletal muscle insulin signaling. The Journal of Nutritional Biochemistry. 2018; 57:35–44. https://doi.org/10.1016/j.jnutbio.2018.03.013 PMID: 29669306.

98. Papazafiropoulou A, Sotiropoulos A, Skliros E, Kardara M, Kokolaki A, Apostolou O, et al. Familial history of diabetes and clinical characteristics in Greek subjects with type 2 diabetes. BMC Endocr Disord. 2009; 9. https://doi.org/10.1186/1472-6823-9-12 PMID: 19397813.

99. Cooke C-LM, Shah A, Kirschenman RD, Quon AL, Morton JS, Care AS, et al. Increased susceptibility to cardiovascular disease in offspring born from dams of advanced maternal age. J Physiol. 2018; 596:5807–21. https://doi.org/10.1113/JP275472 PMID: 29882308.

100. Velaquez MA, Smith CGC, Smyth NR, Osmond C, Fleming TP. Advanced maternal age causes adverse programming of mouse blastocysts leading to altered growth and impaired cardiometabolic health in post-natal life. Hum Reprod. 2016; 31:1970–80. https://doi.org/10.1093/humrep/dew177 PMID: 27402911.

101. Ware S, Voigt J-P, Langley-Evans SC. Body composition and behaviour in adult rats are influenced by maternal diet, maternal age and high-fat feeding. J nutr sci. 2015; 4. https://doi.org/10.1017/jns.2014.64 PMID: 26090100.

102. World Health Organization. Meeting to Develop a Global Consensus on Preconception Care to Reduce Maternal and Child Mortality and Morbidity [cited 23 Jul 2015]. Available from: https://apps.who.int/iris/bitstream/handle/10665/78067/9789241505000_eng.pdf?sequence=1.