Maternal high fiber diet protects offspring on diabetogenic diet in the Nile rat

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Abstract

Type 2 diabetes is strongly associated with both parental history and eating habits. The Nile rat is a model of type 2 diabetes that is highly sensitive to nutritional imbalances. Our aim is to understand the effect of early nutrition derived from maternal diet on the long-term risk of diet-induced diabetes in the offspring.

Using a two-by-two factorial design, 671 Nile rat dams and offspring were randomly fed a high fiber diet or a diabetogenic diet, divided into two developmental stages prior or after weaning. Random blood glucose (RBG) levels were measured every four weeks from 4 to 40 weeks old. To confirm that the observed differences in the progression of RBG is statistically robust, we built a simple Bayesian network using three nodes – maternal diet, offspring diet, and sex.

Among the offspring weaned onto a diabetogenic diet, the influence of maternal diet is remarkable. In these offspring, when the early nutrition is derived from a high fiber maternal diet, the onset of diabetes is delayed by about 16 weeks. Based on our Bayesian modeling, the largest benefit was observed at 36 weeks old with a 48.90% reduced probability of diabetes from 81.77% to 32.87%. This maternal high fiber diet protection effect is more obvious in male than in female offspring. Interestingly, in offspring weaned onto a high fiber diet, maternal diet is irrelevant, and these offspring do not develop type 2 diabetes.

Our study provides evidence that the protective effect of high fiber against type 2 diabetes can be transmitted to the offspring through maternal feeding. Hence, improving maternal nutrition is an effective strategy for the prevention of type 2 diabetes.

Abbreviation

Random blood glucose (RBG)

Introduction

Diabetes is one of the fastest growing health challenges facing us today. In the last 20 years, the number of people living with diabetes increased from 151 million to over 463 million [1]; of those, 90–95% have type 2 diabetes. Type 2 diabetes is a complex disease that is poorly understood. It is characterized by insulin resistance exacerbated by beta cell dysfunction. Lifestyle intervention and current medications including insulin therapy can help regulate blood glucose levels but, in the vast majority of patients, these regimens ultimately fail. Consequently, even with treatment, diabetic patients continue to be at risk for numerous debilitating complications and have approximately a two-fold increased mortality compared to people without diabetes [2]. Hence, prevention of diabetes is a top public health priority around the world.

Diabetic risk is strongly associated with both parental history and eating habits. The odds of developing type 2 diabetes is three- to six-fold higher for adults with at least one diabetic parent compared to adults without parental diabetes [3]. However, genome wide association studies repeatedly reveal that genetic factors insufficiently explain the observed familial aggregation [4, 5], suggesting that familial risk is modulated by nongenetic factors, which might include learned eating behaviors [6, 7] as well as exposure to fetal and neonatal environment [8]. The culpability of diet is well known but not well defined. All three classes of macronutrients – carbohydrate, fat and protein – have been examined quantitatively and qualitatively in the context of type 2 diabetes, but consensus is sorely lacking. In general, newer studies have proposed that a low-carbohydrate diet could be more effective for managing type 2 diabetes compared to a low-fat diet [9, 10]. However, fiber is an exception, unlike simple carbohydrate, fiber is a member of the carbohydrate food group that is associated with a reduced risk of developing type 2 diabetes [11].

Due to the unmistakable familial pattern of type 2 diabetes, parental input is likely part of the etiology. It is suspected that mothers play a major role as the only source of nutrition in the fetal and infant stage. The link between poor maternal nutritional status and detrimental metabolic traits has been consistently reported throughout epidemiology studies [12]. Specifically, the higher risk of type 2 diabetes is associated with adults that had a low birth weight and a catch-up growth during childhood [13, 14]. This correlational data is the basis of the “Fetal Origin of Adult Disease” hypothesis by Barker in the 1990s, which has since expanded into the “Developmental Origins of Health and Disease” paradigm that focuses on nutritional insults during development on adult life disease susceptibility [15]. Experimental studies have similarly demonstrated adverse long-term effects using a maternal malnourished model, frequently using a low protein (in association with higher fat or carbohydrate) diet during gestation and lactation in sheep, pigs, and rodents [16-19]. However, research to date have only focused on the impact of maternal diet in increasing disease susceptibility rather than preventing diabetes. Our study explores the consequence of early nutrition using two opposing maternal diets in shifting the susceptibility of type 2 diabetes.

Here we conducted a longitudinal study of 671 Nile rats *(Arvicanthis Niloticus)* to investigate how maternal diet affects the offspring's diabetic susceptibility. The Nile rat model presents a similar nutritional etiology and disease progression to type 2 diabetes in humans [20-23]. In its natural habitat, Nile rats consume a low energy, high fiber diet and do not develop diet-induced diabetes [22]. However, in captivity, when they eat a high energy, low fiber diet, they become diabetic, and eventually develop human-like long-term diabetic complications such as diabetic retinopathy [24]. In the lifelong susceptibility of type 2 diabetes, both exposure to maternal nutrition and self-acquired nutrition are acting in concert. Previous experimental studies have interrogated maternal diet as an isolated variable [25, 26] but failed to incorporate offspring diet as a covariate. Additionally, we have included sex as a biological variable, acknowledging the presence of sexual dimorphism in diet-induced type 2 diabetes [27, 28]. Using a simple Bayesian network, we incorporated three factors – maternal diet, offspring diet, and sex – in our statistical model to examine the probability of diabetes caused by each factor. Our aim is to provide a definitive study of how maternal diet juxtaposed with offspring diet shifts the long-term risk susceptibility and clarify the role of maternal diet in the prevention of type 2 diabetes.

Methods

Animals

All animal experiments were approved by the University of California Santa Barbara, Institutional Animal Care and Use Committee, and conducted in accord with the NIH Guide for the Care and Use of Laboratory Animals. Our founder Nile rats originated from the Brandeis University colony of the KC Hayes Laboratory. Nile rats in UCSB are housed at 70-78˚F in a conventional facility with individually ventilated cages and are provided autoclaved Sanichips as bedding material.

Experimental Animal Protocol

Nile rat dams are randomly fed a high fiber diet (Lab Diet 5L3M; Newco Speciality, Rancho Cucamonga, CA, USA) or a diabetogenic diet (Formulab Diet 5008; Newco Speciality, Rancho Cucamonga, CA, USA) [22]. Littermates are randomly assigned to either the high fiber or diabetogenic diet, maintained throughout the study. Using sibling-matched diet assignments allow us to redistribute possible genetic bias into each of the high fiber or diabetogenic diet groups. Random blood glucose (RBG) levels are measured every four weeks starting at weaning age (4 weeks old). Diabetic Nile rats are defined as having RBG>100 based on prior studies [29]. To reduce adverse events from diabetic complications, Nile rats with RBG>500 were euthanized. The number of Nile rats grouped by diet scheme and sex is provided in Supplementary Figure S1, and details from each Nile rat are provided in Supplementary Table 1.

Modeling the probability of diabetes

We used a simple Bayesian model framework [30] consisting of three variables (maternal diet, offspring diet, and sex) to model the probability of diabetes from 4 to 40 weeks at 4-week-intervals (Supplementary Figure S2). The Bayesian network parameter learning and probability inference were implemented by R package ("bnlearn") [31].

Estimating human equivalent age of rodents

To provide human relevance, we presented in parallel the human equivalent age of rodents obtained from the Jackson Laboratory (life phases equivalencies between human and mouse) [32].

Results

In a laboratory environment, Nile rats readily develop diabetes when fed a standard rodent chow [22], thereby referred to as a diabetogenic diet (specifically in the context of the Nile rat). Conversely, they do not develop diabetes when fed a high fiber diet. Both diets used are commercial diets based on their robustness to induce and prevent diet-induced diabetes in the Nile rat. In this study, longitudinal RBG measurements were used to access the development and progression of diabetes. Methods of monitoring blood glucose involving fasting were avoided because of the potential confounding effect of regularly fasting our animals in a long-term study. More importantly, RBG has been verified to be a reliable early biomarker and preferred clinical parameter for predicting both incidence of diabetes and its severity in the Nile rat [29].

Offspring on diabetogenic diet were protected against diabetes when mothers consumed a high fiber diet

We observed a large difference between the diabetogenic diet offspring from mothers that consumed a high fiber diet compared to a diabetogenic diet. As shown in Figure 1, in the group where offspring and mothers share the same diabetogenic diets, the average RBG depicts an upward trend from 4 weeks old and clearly reflects a diabetic value from 12 weeks old. The upward trend continues until around 36 weeks old, when the average RBG plateaus at around 300mg/dL. In contrast, in the group with mothers on a high fiber diet, the average RBG wavered around 100mg/dL and did not reach a diabetic value until around 28 weeks, suggesting a delay in onset of diabetes of about 16 weeks. Furthermore, with each subsequent reading at a later timepoint, the difference between the diabetogenic maternal diet group and the high fiber maternal diet group gets larger, suggesting that in addition to the delayed onset of hyperglycemia, the progression of diabetes is additionally slowed down.

Offspring on a high fiber diet did not develop diabetes even when mothers consumed a diabetogenic diet

Interestingly, a high fiber diet conferred long-term protection of offspring against diabetes regardless of maternal diet. In offspring that were fed a high fiber diet after weaning, there was no discernable difference in the average blood glucose trajectory between those that were from mothers with a high fiber diet or those that were from mothers with a diabetogenic diet. The average RBG in both groups never reached the diabetic threshold of RBG>100 mg/dL, from 4 to 40 weeks old (Figure 2). This pattern was observed in both sexes (Supplementary Figure S3).

Protective effect of the high fiber maternal diet was more pronounced in males

The blood glucose lowering effect of the maternal high fiber diet on diabetogenic diet offspring was observed in both sexes. Males benefitted more because they had a more severe hyperglycemic profile compared to the females when on a diabetogenic diet. However, the maternal high fiber diet protection lowered the mean RBG trajectory to a similar normal level in both male and female offspring (Figure 3).

High fiber maternal diet reduced the long-term risk susceptibility of diet-induced diabetes

In our experimental design, we have three factors – maternal diet, offspring diet, and sex – that affect the risk susceptibility of diet-induced diabetes. To account for all three factors, we built a statistical model using a simple Bayesian network from 671 Nile rats with RBG values ranging from 4 to 40 weeks old. From our model, we calculated the probability of diabetes in diabetogenic diet offspring within the high fiber maternal diet group compared to the diabetogenic maternal diet group. As shown in Figure 4, the probability of diabetes in the diabetogenic maternal diet group increased from 28.74% at 12 weeks old (equivalent to 20 years old in a human) to 81.77% at 36 weeks old (equivalent to 38 years old in a human). In comparison, the high fiber maternal diet group increased from 13.21% at 12 weeks old to 32.87% at 36 weeks old. This data is replotted according to sex in Figure 5.

Discussion

Presently, effective prevention measures are needed to curb the steep rising rate of type 2 diabetes. The susceptibility of type 2 diabetes is subjected to cumulative events throughout life, possibly starting from conception, described as a life course perspective. Early life has been identified as a sensitive period of phenotypic plasticity largely modulated by maternal nutrition. Thus, a better understanding of how maternal diet modulates disease susceptibility would inform us on effective ways to prevent type 2 diabetes.

Here, we use two opposing diets that either induce or prevent diabetes in the Nile rat to understand how maternal nutrition shifts the disease risk of type 2 diabetes. Our experimental design is different in a few ways. First, we used a lifelong maternal diet in the dams. In other experimental studies, the maternal diet is typically restricted to pregnancy and lactation.

However, the influence of maternal diet could include the period of oogenesis that occurs preconception. We also considered the possibility that abruptly switching diets just prior to conception may trigger altered behavioral changes due to interrupted eating habits not pertinent to the maternal nutrition. Second, maternal diet and offspring diet were treated as two independent variables, providing us an opportunity to observe the interplay between early life nutrition and later life nutrition. This added layer of information cannot be obtained from studies using maternal diet as the sole experimental variable. Additionally, we considered sex as a biological variable, versus the majority of diabetic studies in animal models where only males are represented. Third, the risk susceptibility of diet-induced diabetes was analyzed in a longitudinal manner. Diet-induced diabetes has a complicated disease profile where onset and severity are highly variable, both in the human population and the Nile rat model. Thus, we generated a detailed longitudinal dataset to capture dynamic changes over time. Also, our dataset for this study is unusually large, consisting of RBG values from 671 Nile rats from 4 to 40 weeks old. This allows us to generate a robust Bayesian model with three nodes: maternal diet, offspring diet, and sex.

We found that a maternal high fiber diet reduces the probability of diabetes in offspring that consumed a diabetogenic diet after weaning (Figure 4). The ratio for the percentage of calories provided by carbohydrate, fat, and protein were 67:10:23 for the high fiber diet and 56:17:27 for the diabetogenic diet. Although the ratios of macronutrients were not dramatically different, the percentage of crude fiber was 23% for the high fiber diet and only 4% for the diabetogenic diet. The beneficial effect of fiber on diet-induced diabetes in the Nile rat had previously been demonstrated by Bolsinger [29]. A recent epidemiological meta-analysis reports a 10–20% reduction in type 2 diabetes incidence associated with higher dietary fiber using data from 48,468 people in 17 studies [33]. The observed protective effect could be due to the presence of dietary fiber that promotes an anti-diabetic microbiome by increasing the amount of short-chain fatty acid [34]. Another possibility is that fiber reduces the intake calories, and the high fiber diet is essentially a low-calorie diet. Future studies using purified diets can be used to assess the specific effects from dietary fiber.

The focus of maternal diet (marker of early life nutrition) stems from observational studies on adults that lived through famines where early life undernutrition was consistently associated with detrimental metabolic health consequences in adult life [35]. To explain these findings, the predictive adaptive response hypothesis was proposed, where a mismatch between early life nutrition and later life nutrition resulted in reduced fitness compared to similarly matched nutrition throughout life [36]. However, a recent human study investigating different combinations of early and later life environmental conditions revealed that adverse early life conditions are detrimental to later health across all environments, not only in mismatched situations [37]. Our two-by-two factorial design provided two groups with mismatched diets and two groups with matched diets. Nile rats with the high fiber maternal diet and diabetogenic offspring diet had a diabetes profile that was better than Nile rats with matched diabetogenic diets but worse than Nile rats with matched high fiber diet. Furthermore, Nile rats with the

diabetogenic maternal diet and high fiber offspring diet did not get diabetes, similar to Nile rats with matched high fiber diets. Therefore, our study does not support the predictive adaptive response hypothesis. Rather, a high fiber diet is beneficial to prevent diabetes whether consumed in early life through the maternal feeding or self-acquired later in life.

In conclusion, we showed compelling evidence that improving maternal nutrition, such as adding high fiber, can be very effective to prevent diet-induced diabetes.

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Authors' relationships and activities

The authors declare that there are no relationships or activities that might bias, or be perceived to be bias, their work.

Contribution statement

JAT and HT designed the study; HT acquired the data; PJ analyzed and interpreted data; HT and PJ wrote the manuscript. All authors revised the manuscript and approved its final version. PJ is the guarantor of this work.

Figure legends

Figure 1: Maternal High Fiber Diet Protects Offspring on Diabetogenic Diet
The progression of diabetes in the Nile rat offspring (both sexes) fed a diabetogenic diet is depicted as a series of random blood glucose levels from 4 to 40 weeks old. The offspring of mothers with a high fiber diet, on average, experienced a delayed onset of diabetes and progressed more gradually to higher levels of RBG compared to offspring of mothers with a diabetogenic diet. The error bars reflect a 95% confidence interval of the data.

Figure 2: Maternal Diet Does Not Influence Offspring on High Fiber Diet
The progression of diabetes in the Nile rat offspring (both sexes) fed a high fiber diet is depicted as a series of random blood glucose levels from 4 to 40 weeks old. When the offspring were fed a high fiber diet, they do not develop diabetes neither from mothers with a high fiber diet nor from mothers with a diabetogenic diet. The error bars reflect a 95% confidence interval of the data.

Figure 3: The Decrease of RBG Trajectory from a Maternal High Fiber Diet was More Obvious in the Male Offspring

A. In male offspring on diabetogenic diet, the protective effect from a maternal high fiber diet was evident from 12 to 40 weeks old. B. In female offspring on diabetogenic diet, the protective effect from a maternal high fiber diet was evident from 24 to 40 weeks old. The error bars reflect a 95% confidence interval of the data.

Figure 4: Offspring Have a Reduced Probability of Diabetes When Mothers Consumed a High Fiber Diet
We used a simple Bayesian network that incorporated maternal diet, offspring diet and sex to calculate the probability of diabetes due to maternal diet differences. When the offspring is on diabetogenic diet, the probability of diabetes is much reduced in the group with a maternal high fiber diet compared to a maternal diabetogenic diet.

Figure 5: The Probability of Diabetes Due to Maternal Diet was Reduced to a Larger Extent in the Male Offspring
A. In male offspring on diabetogenic diet, the ones from mothers on a high fiber diet experienced a reduced probability of diabetes from 8 to 40 weeks old. B. In female offspring on diabetogenic diet, the ones from mothers on a high fiber diet experienced a reduced probability from 25 to 40 weeks old.

List of Supplementary Data

Table S1: Detailed information of Nile rats used in this study including sex, maternal diet, offspring diet and random blood glucose (RBG) levels from 4-40 weeks old. All animals with RBG>500 mg/dL were euthanized for humane reasons. We then transformed all RBG values over 500 mg/dL to 500 mg/dL.

Figure S2: A simple Bayesian network for modeling relative diabetic risk. The nodes structure are pre-defined.

Figure S3: A high fiber offspring's diet can prevent to develop hyperglycemia regardless of mother's diet. (A) The offspring are males; (b) The offspring are females.

Figure 1

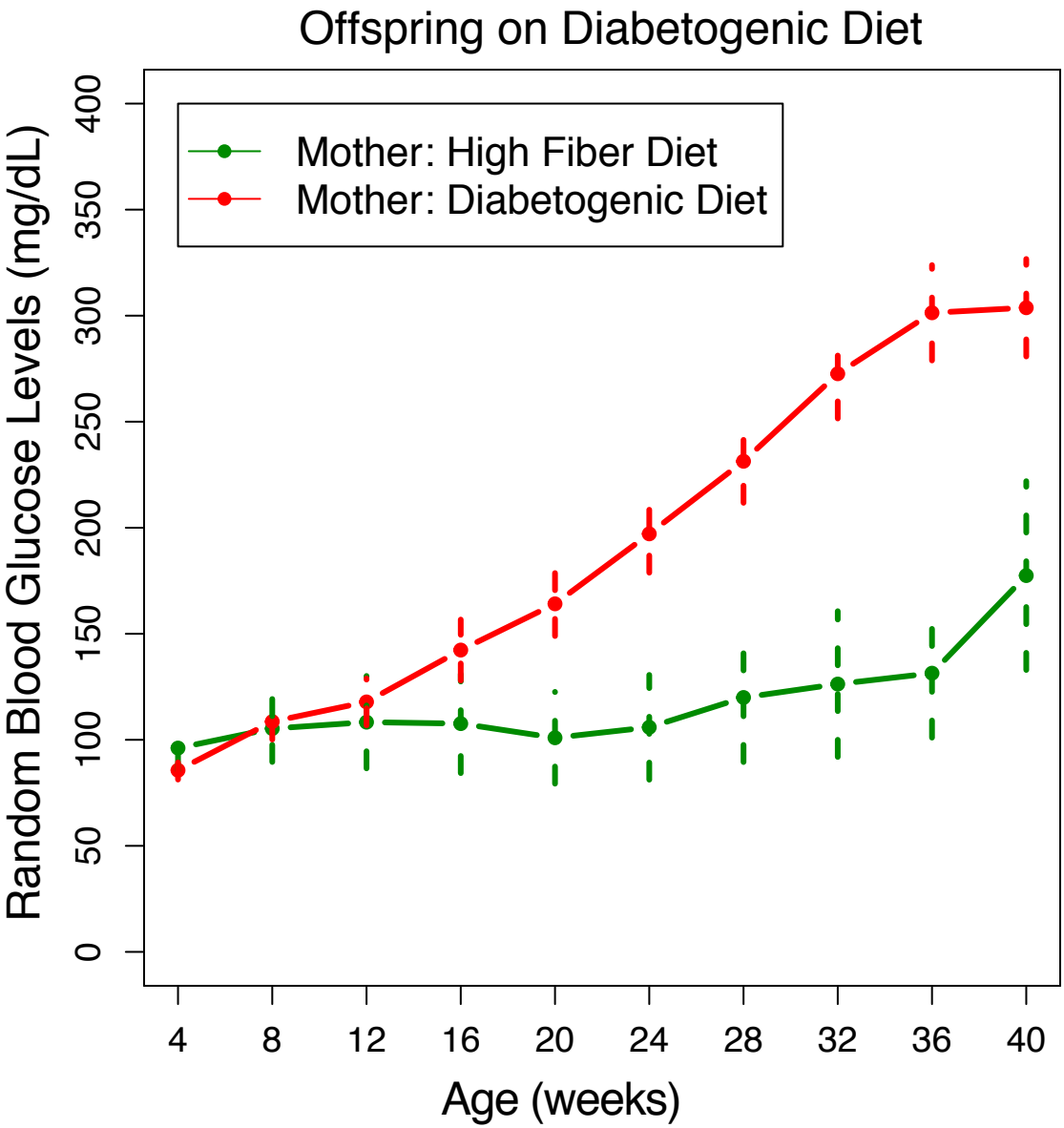

Offspring on Diabetogenic Diet
Mother: High Fiber Diet
Mother: Diabetogenic Diet
Random Blood Glucose Levels (mg/dL)
0
50
100
150
200
250
300
350
400
4
8
12
16
20
24
28
32
36
40
Age (weeks)

Figure 2

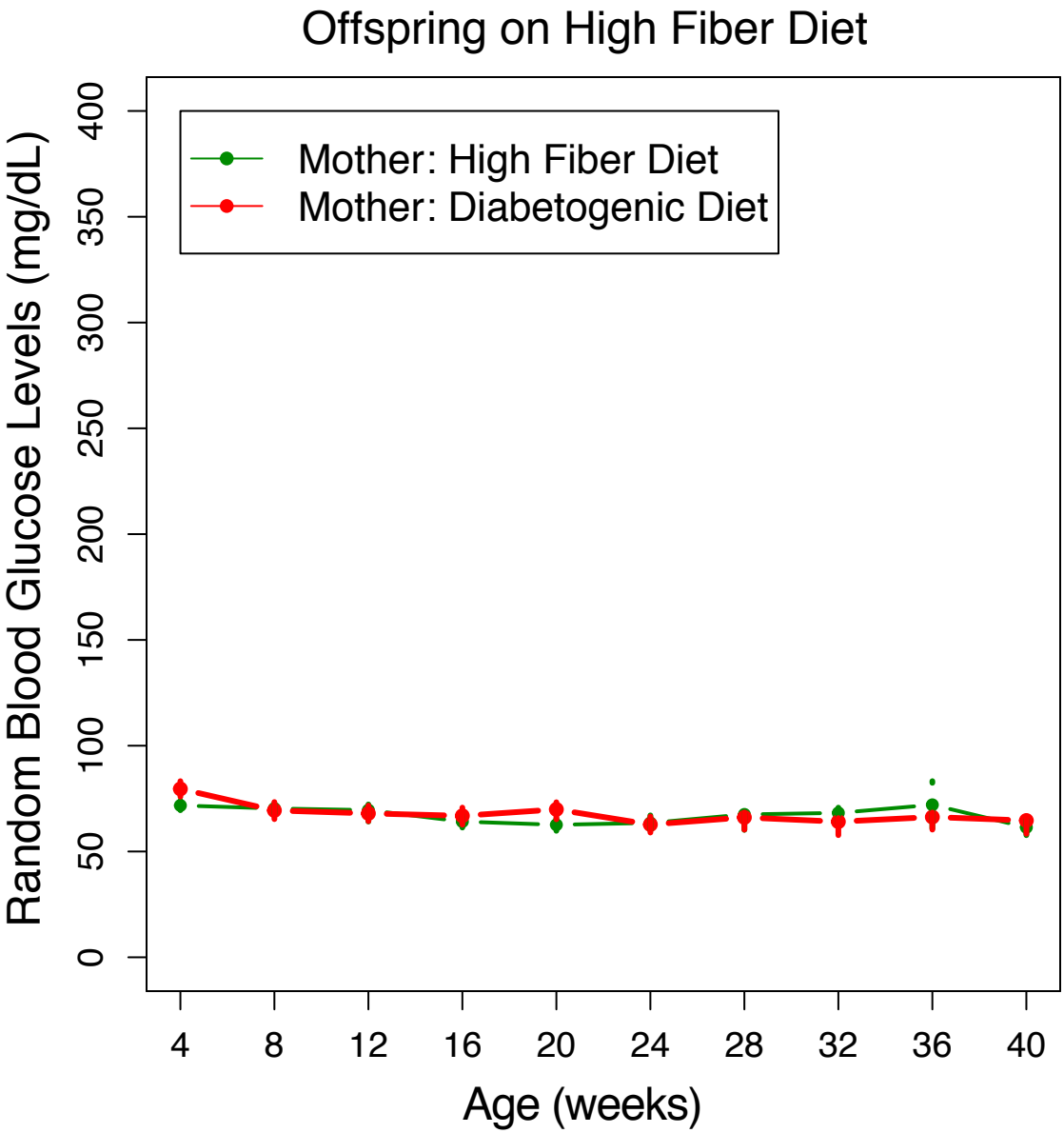

Offspring on High Fiber Diet
Mother: High Fiber Diet
Mother: Diabetogenic Diet
Random Blood Glucose Levels (mg/dL)
0
50
100
150
200
250
300
350
400
4
8
12
16
20
24
28
32
36
40
Age (weeks)

Figure 3

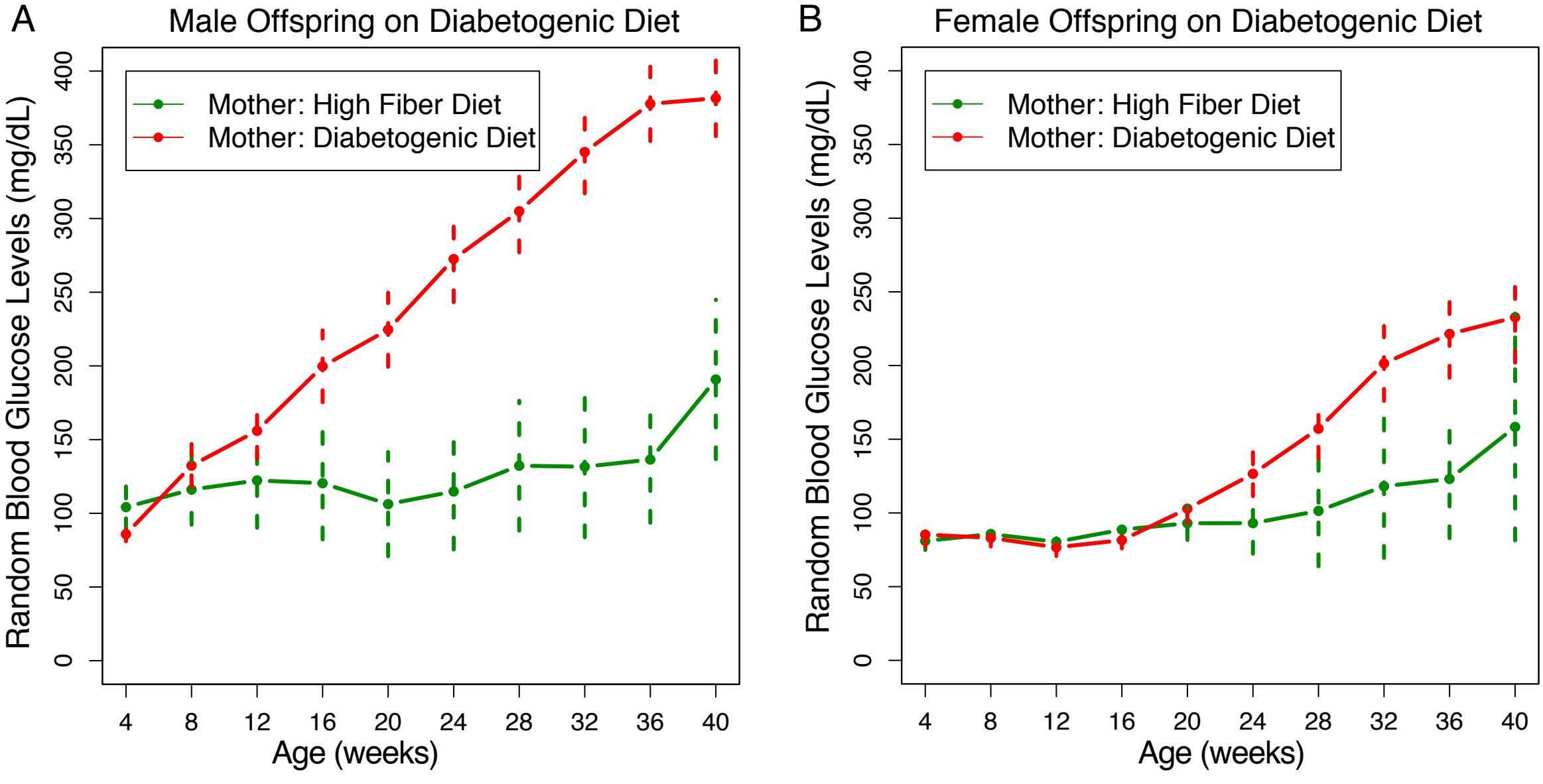

A
Male Offspring on Diabetogenic Diet
Mother: High Fiber Diet
Mother: Diabetogenic Diet
Random Blood Glucose Levels (mg/dL)
0
50
100
150
200
250
300
350
400
4
8
12
16
20
24
28
32
36
40
Age (weeks)
B
Female Offspring on Diabetogenic Diet
Mother: High Fiber Diet
Mother: Diabetogenic Diet
Random Blood Glucose Levels (mg/dL)
0
50
100
150
200
250
300
350
400
4
8
12
16
20
24
28
32
36
40
Age (weeks)

Figure 4

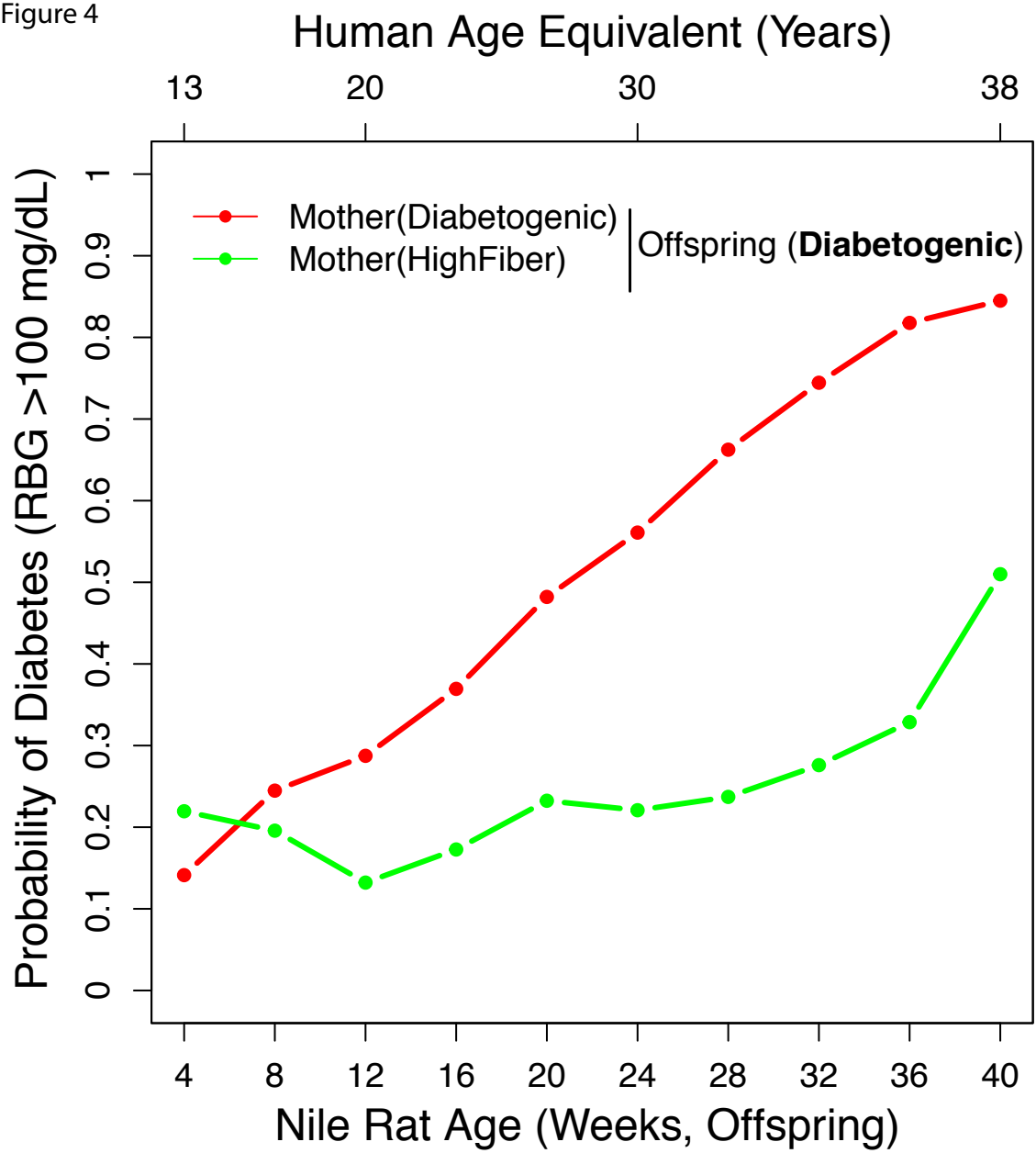
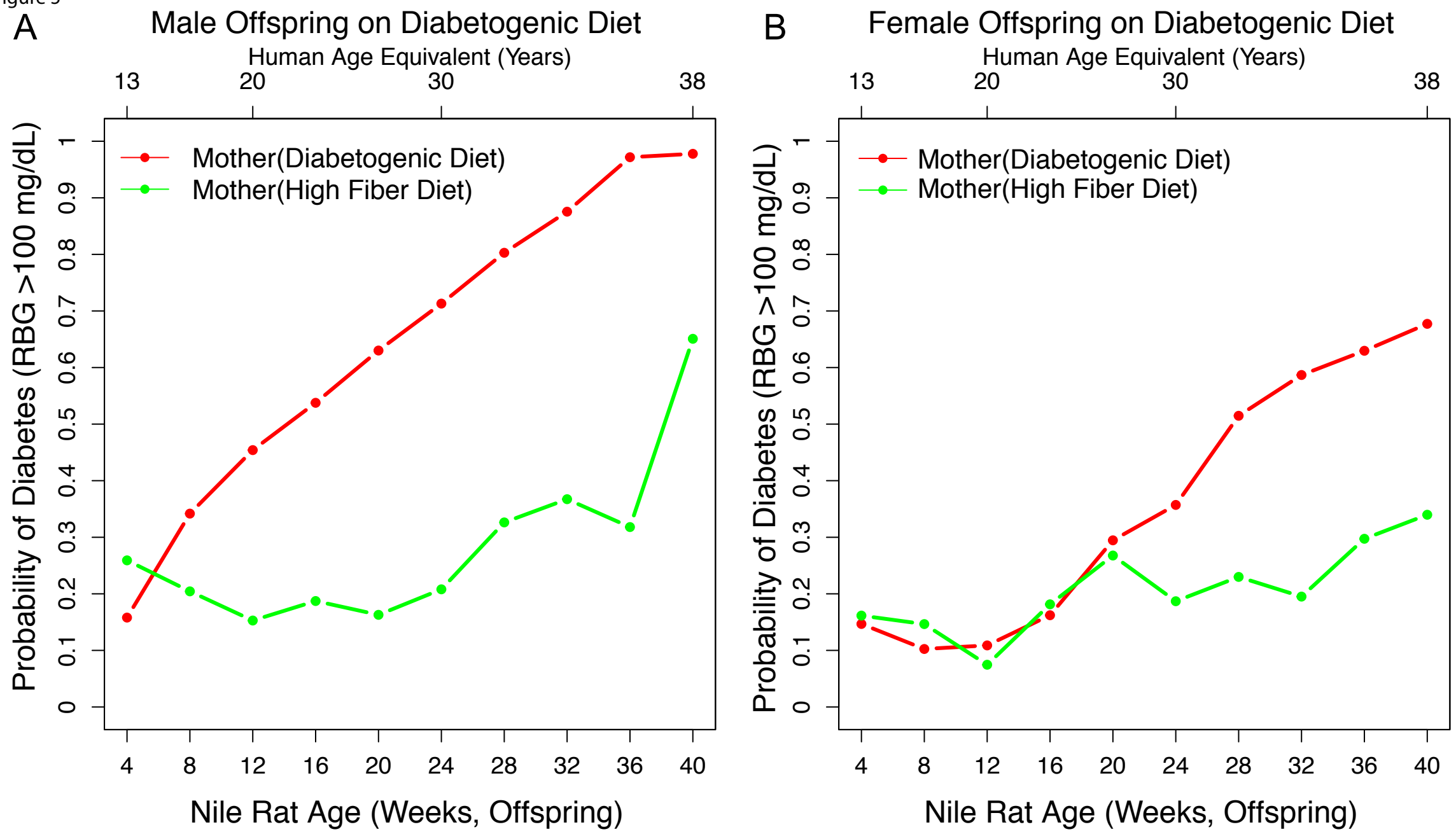

Human Age Equivalent (Years)
13
20
30
38
Mother(Diabetogenic)
Mother(HighFiber)
Offspring (**Diabetogenic**)
Probability of Diabetes (RBG >100 mg/dL)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
4
8
12
16
20
24
28
32
36
40
Nile Rat Age (Weeks, Offspring)

Figure 5


A
Male Offspring on Diabetogenic Diet
Human Age Equivalent (Years)
13
20
30
38
Mother(Diabetogenic Diet)
Mother(High Fiber Diet)
Probability of Diabetes (RBG >100 mg/dL)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
4
8
12
16
20
24
28
32
36
40
Nile Rat Age (Weeks, Offspring)
B
Female Offspring on Diabetogenic Diet
Human Age Equivalent (Years)
13
20
30
38
Mother(Diabetogenic Diet)
Mother(High Fiber Diet)
Probability of Diabetes (RBG >100 mg/dL)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
4
8
12
16
20
24
28
32
36
40
Nile Rat Age (Weeks, Offspring)