

## Supplementary Material\*

Wensink MJ, Lu Y, Tian L, et al. Preconception antidiabetic drugs in men and birth defects in offspring. A nationwide cohort study. *Ann Intern Med.* 29 March 2022. [Epub ahead of print]. doi:10.7326/M21-4389

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\* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

## Statistical Appendix

### Generalized Additive Logistic Regression Model

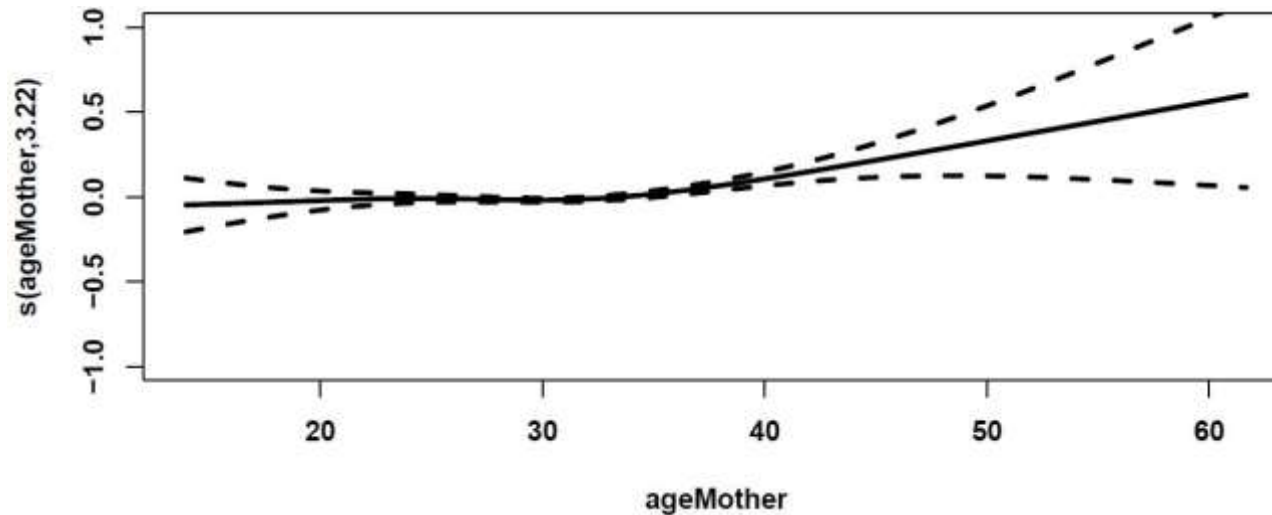
Our use of GAMs was suggested by the fact that some of the potential confounders have a non-linear effect on the logit-transformed risk of birth defects. Specifically, our GAM models the risk of birth defects as

$$\text{logit}(\text{birth defects risk}) = \beta_0 E + f_1(X_1) + \dots + f_p(X_p),$$

which includes the logistic regression model as a special case, and where  $E$  is a binary indicator for the medication exposure of interest,  $X_j$ ,  $1 \leq j \leq p$  are (potential) confounders,  $f_j(\cdot)$  is a function characterizing the effect of  $X_j$ ,  $1 \leq j \leq p$ , and  $\exp(\beta_0)$  is the odds ratio associated with the exposure  $E$ .

In the implementation that we used, R package *mgcv*, the functions  $f_j(\cdot)$  are smoothing spline bases (default option) that are estimated adaptively and may be reduced to a simple linear function as in the common logistic regression when supported by the data. In summary, GAMs allow us to better capture and adjust for confounding. The GAM fitting requires a large sample size, so we took advantage of the over 1 million births in the registry.

As an example of nonlinear confounding effects demonstrated by GAM fitting, the figure below characterizes the effect of maternal age on the logit transformed birth defect risk suggested by the data (>1 million observations, y-axis centered on 0). The GAM selected 3.22 degrees of freedom, 2.22 more than the 1 degree of freedom for a linear impact. A linear function of maternal age would have failed to account for the approximately null effect of age up to age 35, with a progressive increase afterwards. This pattern is in agreement with the literature.



The flexibility provided by the functions  $f_i(\cdot)$  is implemented in *mgcv* by wrapping variables in `s()`, which sets up a scatterplot smoother base. For example, the following R code allows flexible adjustment of birth year, income, and parents' ages via GAM, in addition to other categorical confounding variables.

```
model<-gam(birth defect ~ drug name + s(birth year) +
           education father + s(income father) + s(age father) +
           education mother + smoking status mother + s(age mother),
           data = data,
           subset = liveborn singletons after exclusion criteria,
           family = binomial())
```

The default option, maintained here, is smoothing splines, which have a knot at every observation, with a penalty on the total amount of change accumulated over a variable's domain. The optimal penalty is determined from cross validation. Details can be found in *Statistical Models in S* by Chambers and Hastie and *Generalized Additive Models* by Wood. The use of GAM adjustment in the analysis of covariance has been recommended in the literature (*Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis* (Vol. 3). By Harrell, F.E., 2015)

## Clustering by father

To account for clustering by father, we set up a wild bootstrapping algorithm that accounted for such clustering without imposing any particular correlation structure. To mimic the conventional bootstrap which assigns random multinomial weights with mean 1 and variance 1 to each birth, our wild bootstrap procedure assigns the same unit exponential random weight (also having a mean 1 and variance 1) to all births sharing the same father.

For each of the  $i = 1, \dots, 10$  imputed data sets, the complete datasets were obtained:

```
Data.i <- complete(mids object, i)
```

The following algorithm (with a simulated data set) was then adjusted to the data:

```
#####
```

```
### Y is binary outcome
```

```
### X1 is the medication; X2 and X3 are confounders to adjust; father is id for fathers (should be integer, can be obtained through as.integer(as.factor(father)) if father is character, or through:
```

```
## Index father id by "1, 2, 3, ... "
```

```
father.id=unique(father)
```

```
n.father=length(father.id)
```

```
father.new=rep(NA, n)
```

```
for(i in 1:n)
```

```
  father.new[i]=(1:n.father)[father[i]==father.id]
```

```
### generate data for demonstration purposes
```

```
n=500
```

```
x1=rbinom(n, 1, 0.2)
```

```
x2=rnorm(n)
x3=rexp(n)
father=sample(n, n, T)
odds=exp(-0.5+x1+0.5*log(x3))
prob=odds/(1+odds)
y=rbinom(n, 1, prob)

#####

## Main analysis
fit=gam(y~x1+s(x2)+s(x3), family="binomial")
beta0=fit$coef[2] # can by multiple coefficients if need be
# Will give warning of non-integer number of outcomes due to wild bootstrap. Can be ignored.

## Wild Bootstrap
## Fix the penalty parameter so save running time
sp0=fit$sp

## run 100 bootstraps ###
n=length(y)
B=100
beta.boot=rep(NA, B)
for(b in 1:B)
```

```

{set.seed(b)
weight=rexp(n) # exponential distribution with parameter 1 has mean and variance 1.
weight.boot=weight[father]
fit.bt=gam(y~x1+s(x2)+s(x3), sp=sp0, weight=weight.boot, family="binomial")
beta.boot[b]=fit.bt$coef[2] # again, can be multiple coefficients if need be
print(b)
}
# Will give warnings of non-integer number of outcomes due to wild bootstrap. Can be ignored.
# On ~1 million births, the mean weights will be very close to 1 (law of large numbers)

## The histogram should be normal with its center around "beta0"
hist(beta.boot)
lines(rep(beta0, 2), c(0, 100), col=2)

## summary the standard error estimates accounting for correlations
se.beta=sd(beta.boot)

#####

```

On a computational note, working with the 10 completed data sets rather than with the `mids` object has the advantage that 10 computing tasks (or 5, or 2) can be set up in parallel.

## Running GAMs on the imputed data

First, GAM models above were fit for each of the 10 imputed datasets and the point estimator of the adjusted odds ratio (AOR), and its standard error estimate based on wild bootstrap were obtained. Then, we pooled the resulted estimates using Rubin's rule:

Pooled point estimate = mean estimate over 10 datasets

Pooled variance estimate of the pooled point estimate = mean variance estimate of over 10 datasets + 1.1 \* variance of 10 point estimates

We implemented Rubin's rules to calculate the final point estimate for  $\log(\text{AOR})$  and its variance. A Wald-type confidence interval for the  $\log(\text{AOR})$  associated with the exposure was then calculated by assuming a Normal distribution for the point estimator based on large sample approximations.

Supplement Table 1. Populating the model with potential confounders. Results in the main manuscript are from the bootstrapped version of model 5.

a) Variables included in each of the models. Parental birth defects are any time in the period, before and after birth of their offspring.

	Year	Father attributes: age, education, income	Mother attributes: age, education, smoking	Parental birth defects	Nulliparity	Preconception diabetes diagnoses	Cardiovascular drugs and antidepressants
Model 1							
Model 2	X						
Model 3	X	X					
Model 4	X		X				
Model 5	X	X	X				
Model 6	X	X	X	X			
Model 7	X	X	X	X	X		
Model 8	X	X	X			X	
Model 9	X	X	X				X

b) Adjusted odds ratios of the drug variables for insulins, metformin, sulfonylureas, and other diabetes drugs, all in one model. Reported are adjusted odds ratios with 95% confidence intervals. Birth year was the only variable that changed the coefficients materially. Nulliparity, birth defects of each of the parents, and low maternal education were all highly predictive of birth defects ( $p < 0.001$  with large coefficients for the former two), but did not change the coefficients of the drug variables. Results from GAMs assuming independence (i.e., do not account for clustering by father) as we merely wished to see the direction of the point estimate, which is unbiased also for unclustered analyses.

	Insulins	Metformin	Sulfonylureas	Other orals
Model 1	0.99 (0.85 – 1.15)	1.57 (1.21 – 2.02)	1.30 (0.89 – 1.89)	0.74 (0.37 – 1.46)
Model 2	0.98 (0.85 – 1.15)	1.44 (1.12 – 1.86)	1.38 (0.95 – 2.01)	0.68 (0.34 – 1.33)
Model 3	0.98 (0.85 – 1.14)	1.42 (1.10 – 1.83)	1.37 (0.94 – 2.00)	0.67 (0.34 – 1.33)
Model 4	0.98 (0.84 – 1.14)	1.40 (1.09 – 1.81)	1.35 (0.93 – 1.97)	0.67 (0.34 – 1.32)
Model 5	0.98 (0.84 – 1.14)	1.41 (1.09 – 1.81)	1.36 (0.94 – 1.99)	0.67 (0.34 – 1.33)
Model 6	0.98 (0.85 – 1.15)	1.41 (1.10 – 1.82)	1.35 (0.93 – 1.97)	0.67 (0.34 – 1.32)
Model 7	0.99 (0.85 – 1.15)	1.43 (1.11 – 1.84)	1.35 (0.93 – 1.97)	0.66 (0.33 – 1.31)
Model 8	1.00 (0.74 – 1.35)	1.49 (1.14 – 1.97)	1.43 (0.97 – 2.11)	0.70 (0.35 – 1.40)
Model 9	0.98 (0.84 – 1.14)	1.41 (1.09 – 1.83)	1.35 (0.93 – 1.97)	0.68 (0.34 – 1.34)



Supplement Table 2. Adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) for a regression including various classes of cardiovascular drugs and antidepressants. This is model 9 of Supplement Table 1. Birth defects that were elevated for betablockers included heart defects and various other categories.

	OAR (95% CI)
<i>Insulins</i>	0.98 (0.84 – 1.14)
<i>Metformin</i>	1.41 (1.09 – 1.83)
<i>Sulfonylureas</i>	1.35 (0.93 – 1.97)
<i>Betablocker *</i>	1.25 (1.06 – 1.47)
<i>Diuretic †</i>	1.18 (0.91 – 1.51)
<i>Calcium channel blocker ‡</i>	0.94 (0.76 – 1.17)
<i>ACE inhibitor or similar §</i>	1.05 (0.91 – 1.22)
<i>Lipid-modifying agent   </i>	0.91 (0.77 – 1.09)
<i>Antidepressant ¶</i>	0.95 (0.87 – 1.03)

\*All ATC C07

† All ATC C03

‡ All ATC C08

§ All ATC C09

|| All ATC C10

¶ All ATC N06A

Supplement Table 3. Timeframe analysis. Birth characteristics by timing of metformin exposure. Columns overlap.

	>1 year before (n=1,861)	1 year before (n=1,751)	sperm development (n=1,451)	1 year after (n=2,484)	>1 year after (n=28,112)
Age mother, years, Q2 (Q1 – Q2)	33.4 (29.8 – 37.3)	33.3 (29.9 – 37.3)	33.4 (30.0 – 37.5)	33.1 (29.6 – 37.1)	31.2 (27.5 – 34.9)
Low education mother (n)	31% (520)	32% (499)	32% (413)	32% (704)	33% (8,637)
Mother smoked during pregnancy (n)	12% (218)	11% (194)	11% (159)	12% (298)	19% (4,497)
Age father, years, Q2 (Q1 – Q2)	40.2 (35.0 – 46.3)	40.1 (35.2 – 46.3)	40.3 (35.6 – 46.3)	39.8 (34.9 – 45.7)	35.8 (31.5 – 40.6)
Low education father (n)	33% (562)	33% (534)	32% (429)	32% (735)	33% (8,677)
Paternal income, 1,000 DKK, Q2 (Q1 – Q3)	175 (123 – 242)	172 (123 – 239)	172 (123 – 236)	167 (121 – 235)	146 (108 – 193)
Father on betablocker (n) *	4.3% (80)	4.9% (86)	5.4% (78)	4.4% (109)	1.5% (416)
Father on diuretic (n) †	3.3% (62)	4.0% (70)	4.5% (66)	3.3% (81)	1.1% (311)
Father on calcium channel blocker (n) ‡	5.2% (97)	5.8% (102)	6.9% (100)	5.2% (128)	1.3% (374)
Father on ACE inhibitor or similar (n) §	19% (360)	21% (376)	25% (369)	18% (448)	3.4% (967)
Father on lipid-modifying agent (n)	24% (448)	28% (492)	34% (493)	23% (560)	3.0% (856)
Father on antidepressant (n) ¶	4.8% (90)	5.7% (100)	6.7% (97)	5.9% (147)	2.7% (767)
Gestational age, days, Q2 (Q1 – Q3)	279 (273 – 286)	278 (272 – 286)	278 (273 – 286)	278 (273 – 286)	278 (273 – 287)
Nulliparity (n)	31% (583)	31% (546)	31% (451)	33% (828)	36% (10,032)
Birth weight, kg, Q2 (Q1 – Q3)	3.5 (3.1 – 3.8)	3.5 (3.1 – 3.8)	3.5 (3.1 – 3.8)	3.5 (3.1 – 3.8)	3.5 (3.1 – 3.8)
Birth length, cm, Q2 (Q1 – Q3)	52 (50 – 53)	52 (50 – 53)	52 (50 – 53)	52 (50 – 53)	52 (50 – 53)
Major birth defect (n)	4.0% (74)	4.4% (77)	5.2% (75)	4.3% (107)	3.3% (921)
Male sex (n)	49.7% (925)	49.7% (871)	49.4% (717)	49.8 (1,237)	51.3% (14,412)

Q1 = first quartile, Q2 = second quartile (median), Q3 = third quartile

n = number

DKK = Danish crowns

\*All ATC C07

† All ATC C03

‡ All ATC C08

§ All ATC C09

|| All ATC C10

¶ All ATC N06A