

Supporting Information

Table S1. Contributing centers and provided data.

Contributing centers	Provided case data (N)	Prospective included cases (N)	Retrospective included cases (N)	Excluded cases (N)
All centers	209	175	22	12
Australia <i>MotherSafe, Sidney</i>	10	8	1	1^a
France <i>French Network of Pharmacovigilance Centers, Terappel</i>	99	78	14	7
<i>Centre de Référence sur les Agents Tératogènes, Paris</i>	35	32	3	0
	64	46	11	7 ^b
Germany <i>Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy, Berlin</i>	29	24	5	0
Israel <i>The Israeli Teratology Information Service, Jerusalem</i>	16	15	1	0
Italy <i>Centro di Riferimento Regionale di Tossicologia Perinatale, Firenze</i>	4	4	0	0
<i>Teratology Information Service, Telefono Rosso, Catholic University of Sacred Heart, Rome</i>	1	1	0	0
<i>TIS PADUA-CEPIG, Clinical Genetics Unit, Department of Women's and Children's Health, University of Padua</i>	2	2	0	0
	1	1	0	0
Japan <i>Japan Drug Information Institute in Pregnancy (JDIIP), Tokyo</i>	5	5	0	0
Netherlands <i>Teratology Information Service of the Netherlands Pharmacovigilance Centre Lareb</i>	2	1	0	1^c
Spain <i>Clinical Pharmacology Service, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, TIS Barcelona</i>	10	10	0	0
	1	1	0	0

<i>Servicio de Información Telefónica sobre Teratógenos Español (SITTE) – Service for health professionals, Madrid</i>	9	9	0	0
Switzerland <i>Swiss Teratogen Information Service, Division de Pharmacologie Clinique, Centre hospitalier universitaire vaudois, Lausanne</i>	5	5	0	0
Turkey <i>Medical Pharmacology Outpatient Clinics, Marmara University Education and Research Hospital, Istanbul</i>	11 3	10 3	0 0	1 0
<i>Terafar – Izmir Katip Celebi University Teratology Information, Training and Research Center, Izmir</i>	4	3	0	1 ^c
<i>Trabzon-TIS — Teratology Information Service, Department of Pharmacology, Karadeniz Technical University, Trabzon</i>	4	4	0	0
United Kingdom <i>UK Teratology Information Service, Newcastle upon Tyne</i>	13	12	1 (twin pregnancy)	0
USA <i>MotherToBaby, Center for Better Beginnings, University of California San Diego</i>	5	3 (including one twin pregnancy)	0	2 ^d

^a Exclusion because estimated date of birth was after August 1st, 2019. ^b Exclusion of four cases because crucial data were missing, exclusion of three cases as duplicates to other French cases. ^c Exclusion because of preconceptional exposure only. ^d Exclusion because of preconceptional exposure only in one case, exclusion of another because crucial date were missing.

Table S2. Reference charts for neonatal growth parameters.

Country and center	Type of growth chart and references ¹
Australia <i>MotherSafe, Sidney</i>	International tool: (Villar et al., 2014) and (Villar et al., 2015), underlying data can be accessed via https://intergrowth21.tghn.org/standards-tools/
France <i>French Network of Pharmacovigilance Centers, Terappel</i> <i>Centre de Référence sur les Agents Tératogènes, Paris</i>	Country-specific tool: https://www.audipog.net/Courbes-morpho , brief summary of methods on the website and in (Vendittelli, Rivière, Pinquier, & Claris, 2008)
Germany <i>Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy, Berlin</i>	Publication: (M. Voigt et al., 2014) ²
Israel <i>The Israeli Teratology Information Service, Jerusalem</i>	Publication: (Dollberg, Haklai, Mimouni, Gorfein, & Gordon, 2005) ²
Italy <i>Centro di Riferimento Regionale di Tossicologia Perinatale, Firenze</i> <i>TIS PADUA-CEPIG, Clinical Genetics Unit, Department of Women's and Children's Health, University of Padua</i> <i>Teratology Information Service, Telefono Rosso, Catholic University of Sacred Heart, Rome</i>	Country-specific tool: (Bertino et al., 2010), underlying data can be accessed via http://www.inescharts.com/
Japan <i>Japan Drug Information Institute in Pregnancy (JDIIP), Tokyo</i>	Country-specific tool: (Itabashi et al., 2010), underlying data can be accessed via http://jspe.umin.jp/medical/keisan.html ³
Netherlands <i>Teratology Information Service of the Netherlands Pharmacovigilance Centre Lareb</i>	Publication: (Hoftiezer et al., 2019) ² , underlying data can be accessed via https://www.perined.nl/geboortegewichtcurven
Spain <i>Clinical Pharmacology Service, Vall d'Hebron Hospital Universitari, Vall d'Hebron Barcelona Hospital Campus, TIS Barcelona</i> <i>Servicio de Información Telefónica sobre Teratógenos Español (SITTE) – Service for health professionals, Madrid</i>	Publication: (Generalitat de Catalunya Departament de Salut, 2008) ^{2,4} , accessible via https://scientiasalut.gencat.cat/bitstream/handle/11351/1209/corbes_referencia_pes_londgitu_d_nounats_catalunya_2010.pdf?sequence=1
Switzerland <i>Swiss Teratogen Information Service, Division de Pharmacologie Clinique, Centre hospitalier universitaire vaudois, Lausanne</i>	Publication: (M Voigt et al., 2006) ⁵ , see also https://cdn.paediatrieschweiz.ch/production/uploads/2020/05/Perzentilen_2012_09_15_SGP_d-1.pdf

Turkey <i>Medical Pharmacology Outpatient Clinics, Marmara University Education and Research Hospital, Istanbul</i>	Publication: (Kurtoğlu et al., 2012)
<i>Terafar – Izmir Katip Celebi University Teratology Information, Training and Research Center, Izmir</i>	
<i>Trabzon-TIS — Teratology Information Service, Department of Pharmacology, Karadeniz Technical University, Trabzon</i>	
United Kingdom <i>UK Teratology Information Service, Newcastle upon Tyne</i>	Publication: (Cole, Williams, & Wright, 2011)
USA <i>MotherToBaby, Center for Better Beginnings, University of California San Diego</i>	International tool: (Villar et al., 2014) and (Villar et al., 2015), the underlying data can be accessed via https://intergrowth21.tghn.org/standards-tools

¹ Country-specific reference standards provided SDS either directly or indirectly by a precise quantile (France, Italy, Japan), or they provided the parameters (or data to approximate the parameters) for applying the LMS method by Cole (Cole & Green, 1992), as in the reference standards for Germany, Israel, Netherlands, Spain, Switzerland, Turkey and UK. The LMS method is a transformation from skewed data to standard normal, using the three parameters skewness (L), median (M) and coefficient of variation (S). Last date of access for web-based tools or data: 28 April 2023. ² Without LMS parameters, but including data to approximate the parameters for the LMS method. ³ Data accessed on 8 June 2022; version 1.1 was used for study cases. ⁴ Growth parameters were collected in Catalonia only. In this study, they were used for all Spanish study cases. ⁵ Statistical methodology uses normal distribution.

References regarding neonatal growth charts in Table S2

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Table S3. SDS means for birth weight (BW) and neonatal head circumference (HC) based on international vs. country-specific reference charts.

SDS means for BW and neonatal HC based on international (Intergrowth-21st) vs. country-specific reference charts show large differences. In Japanese newborns, for example, the difference of SDS means for BW amounts to +0.74 SDS, the difference of SDS means for HC to +0.42 SDS. In other words, SDS means of Japanese growth parameters in the cohort analyzed here are much higher if based on country-specific reference standards than if based on Intergrowth-21st standards. For infants from most other countries the opposite is true: SDS means are considerably smaller if based on country-specific reference standards. For example, the SDS mean for BW in German newborns is -0.34 SDS smaller according to country-specific reference charts than according to Intergrowth-21st, and the SDS mean for HC decreases by -0.9 SDS.

COUNTRY	Birth weight: SDS ¹ mean				Neonatal head circumference: SDS ¹ mean			
	Cases (N)	International reference charts	Country-specific reference charts	Difference	Cases (N)	International reference charts	Country-specific reference charts	Difference
Australia	4	+0.46	N/A	N/A	4	+0.08	N/A	N/A
France	64	-0.12	-0.22	-0.10	31	+0.24	-0.21	-0.45
Germany	20	-0.16	-0.50	-0.34	19	+0.41	-0.49	-0.90
Israel	14	-0.35	-0.26	+0.09	0	N/A	N/A	N/A
Italy	2	-1.22	-1.49	-0.27	1	+0.44	+0.28	-0.16
Japan	5	-0.06	+0.69	+0.74	5	+0.12	+0.54	+0.42
Netherlands	1	-0.06	-0.65	-0.58	0	N/A	N/A	N/A
Spain	10	-0.55	-0.56	-0.01	4	-0.18	-0.45	-0.28
Switzerland	5	+0.13	-0.25	-0.37	3	+1.48	+0.44	-1.04
Turkey	6	+0.85	+0.94	0.09	1	+3.04	+2.44	-0.60
UK	9	-0.29	-0.37	-0.07	2	-0.06	-0.32	-0.26
USA	4	-0.26 ²	N/A	N/A	3	+0.91 ²	N/A	N/A

¹ SDS: Standard deviation score. ² Since reference charts for twins were not available, percentiles for one set of twins were calculated according to singleton reference charts. If they are excluded from the analysis, SDS mean for BW (N=2) is -0.83 and for neonatal HC (N=1) -0.18.

Table S4. Overview of prospectively ascertained study cases included for defined outcomes.

	Study inclusion criteria	N
All prospectively ascertained cases	Any exposure to modafinil between 2+0 weeks after last menstrual period and delivery. Estimated date of birth (EDOB) before August 2019. Data on pregnancy outcome and congenital malformations available.	175 pregnancies
Outcome analysis	Additional criteria for inclusion in specific analysis	N
Cumulative incidences of pregnancy outcome	Start of modafinil exposure before study entry.	174 pregnancy outcomes
Major congenital malformations (MCA)	First trimester exposure to modafinil. No diagnosed chromosomal/genetic disorder of the fetus/newborn. Fetus affected with MCA or live birth.	150 pregnancy outcomes
Percentile values and standard deviation scores (SDS) for birth weight (BW)	Live birth. Measurement of BW available. Data on gestational age at birth and neonatal sex available.	144 newborns
Percentile values and standard deviation scores (SDS) for neonatal head circumference (HC)	Live birth. Measurement of neonatal HC available. Data on gestational age at birth and neonatal sex available.	73 newborns
Potential dose-dependent effects on BW	Live birth. Measurement of BW available. Data on cumulative modafinil dosage, gestational age at birth and neonatal sex available.	121 newborns
Potential dose-dependent effects on HC	Live birth. Measurement of neonatal HC available. Data on cumulative modafinil dosage, gestational age at birth and neonatal sex available.	59 newborns
Postnatal Growth	Live birth. Modafinil exposure in all three trimesters. At least one measurement of weight and HC after the first month of life. Data on gestational age at birth and infant sex available.	4 infants

Table S5. Infants with major congenital anomalies (MCA).

Pregnancy outcome, completed GW¹ at delivery, sex	Modafinil exposure (GW¹; dosage)	Indication for modafinil treatment	Major congenital anomalies (MCA)², additional minor anomalies and/or remarks
Live birth, GW 41, male	GW 0 – 5+4; 400 mg/d	Idiopathic hypersomnia	Unilateral foot malformation: cutaneous syndactyly (4th-5th toes) and supernumerary metatarsal bone. Mild facial dysmorphism, jaw-winking. Epidermoid cyst in skull bone. Orbital cyst. Bilateral inguinal hernia. Relevant vesicoureteral reflux. Genetic testing provided unremarkable results.
Live birth, GW 41, female	GW 0 – 39+3; during 1 st trimester 200 mg/d	Narcolepsy	Pierre Robin sequence with retrognathia, glossoptosis and cleft palate. Metatarsus varus.
Live birth, GW 38, female	GW 0 – 2+3; 300 mg/d	Narcolepsy	Esophageal atresia. Neonatal death within the first week of life.

¹ GW: gestational weeks. ² None of the affected newborns was exposed to concurrent medication with known teratogenic effects. Study cases with chromosomal aberrations are not included.

Figure S1

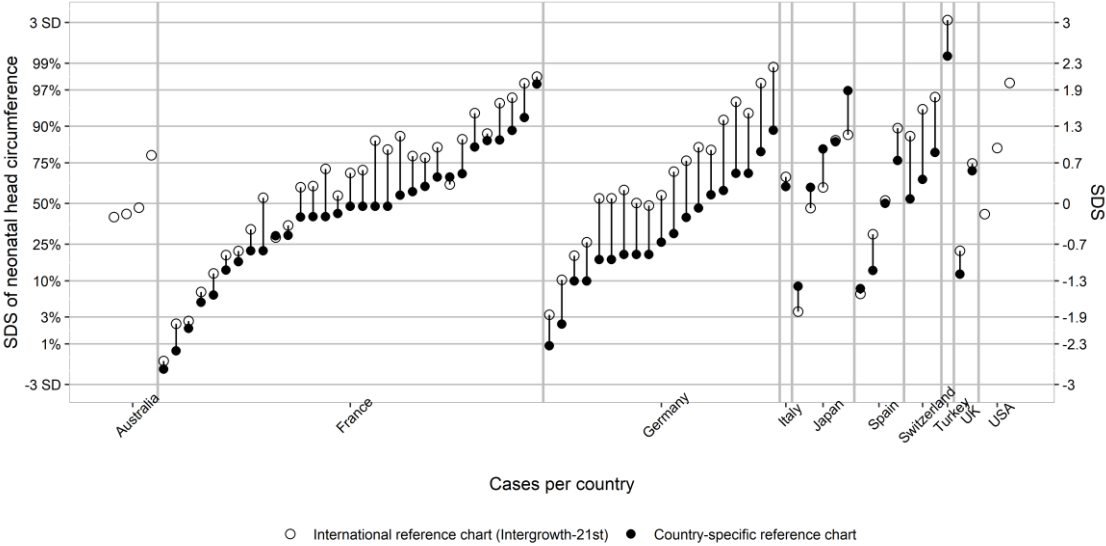


Figure S1. Standard deviation scores (SDS) and percentiles (in %) of individual neonatal head circumference (HC) in different countries according to international (Intergrowth-21st) vs. country-specific reference charts. No severe microcephaly (head circumference less than -3 SD) was detected, regardless of whether country-specific or international percentiles were used.

Figure S2

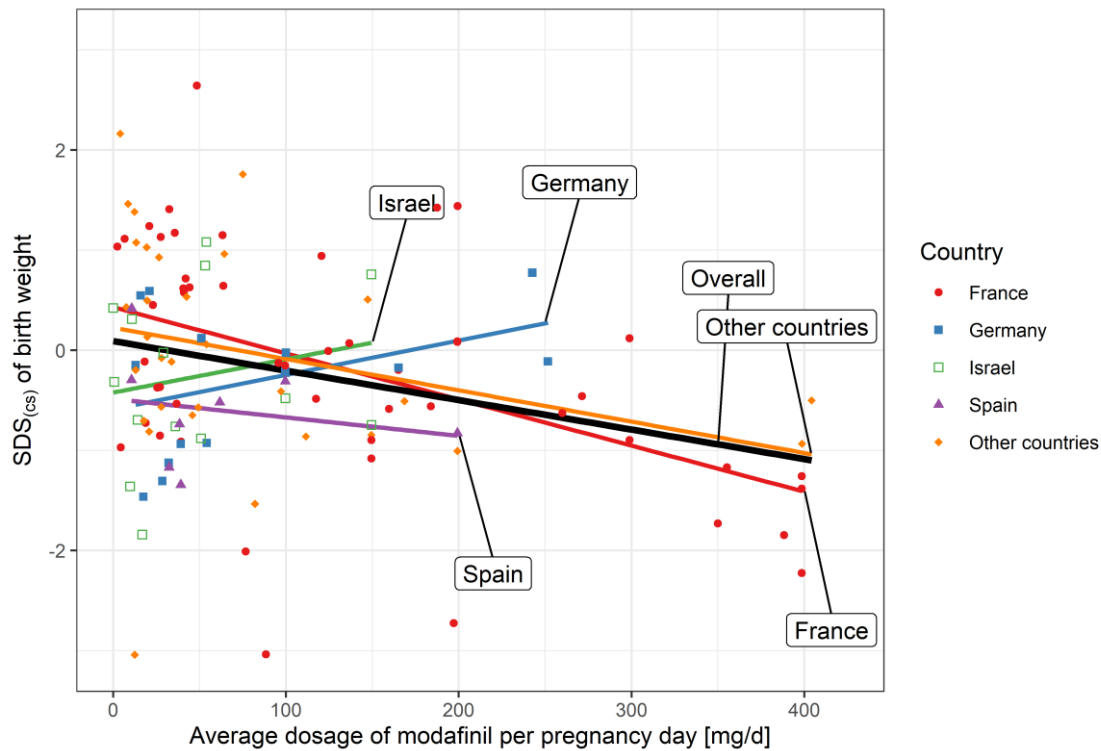


Figure S2. Potential dose-dependent effects of modafinil on birth weight (BW): Country-specific and overall correlations in a linear regression model. For statistical details of this model, see Table S6 (presented below Figure S3). The **black line** represents the regression line for all cases combined (N=121). Other countries refers to all countries with less than ten observations for BW and country-specific reference charts, i.e. Italy, Japan, Netherlands, Switzerland, Turkey and United Kingdom. SDS(cs): Standard deviation scores based on country-specific reference charts taking into account neonatal sex and GW at delivery. If an average dosage per pregnancy day of zero (i.e. no modafinil exposure) is assumed, the model obtains an overall SD score of 0.054 for BW (95% CI, -0.2 to 0.3). For all countries combined, a decreasing slope is obtained, also for France, Spain and the group of countries contributing less than ten cases. In contrast, the slope is increasing for Germany and Israel. If the findings for Germany are compared to France, the slope increases by the factor 0.77 SDS (France -0.43, Germany +0.34, 95% CI, 0.07 to 1.48) with each 100 mg increase of average dosage per pregnancy day. However, the main reason for this effect are the SDS differences in cases with low dosages per pregnancy day: In these cases, the SDS of BW are considerably lower in Germany than in France, resulting in a considerably lower intercept. In fact, the intercept of Germany (i.e. the SDS for BW with an assumed modafinil exposure of zero) is lowered by -0.91 SDS (France: 0.32, Germany: -0.61, 95% CI, -1.77 to -0.05). The data for Israel are similar, but results lack statistical significance due to low sample size. Furthermore, Germany (as well as Israel) contributed no cases with very high (≥ 300 mg) average dosages per pregnancy day. In an additional model, we eliminated the impact of sample-specific intercept differences between countries by using the same intercept for each country (see Figure S3).

Figure S3

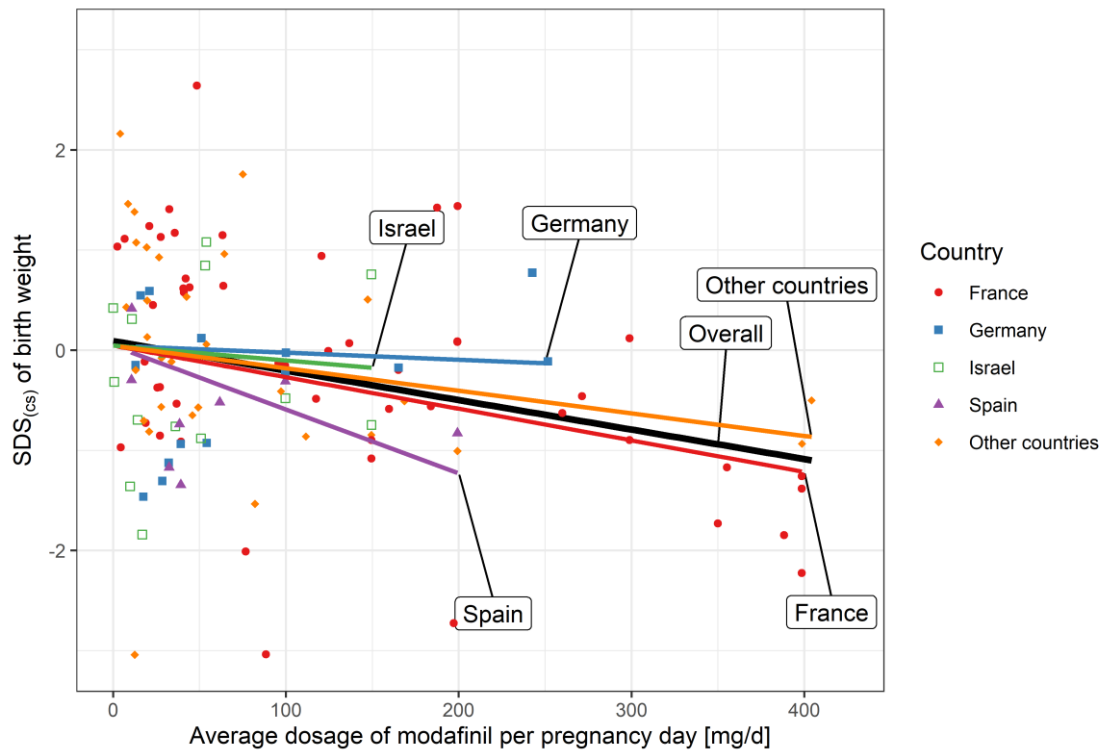


Figure S3. Potential dose-dependent effects of modafinil on birth weight (BW): Additional linear regression model to eliminate the impact of sample-specific intercept differences between countries. For each country, the same intercept is used, i.e. 0,043 SDS. The **black line** represents the regression line for all cases combined (N=121). In this model, the slopes of Germany and Israel no longer increase and the differences between France and Germany are no longer significant. For statistical details of this model, see Table S6 (presented below this Figure). Other countries refers to all countries with less than ten observations for BW and country-specific reference charts, i.e. Italy, Japan, Netherlands, Switzerland, Turkey and United Kingdom. SDS(cs): Standard deviation scores based on country-specific reference charts taking into account neonatal sex and GW at delivery.

Table S6. Coefficient tables and summary statistics for the linear models of potential dose-dependent effects on birth weight (for Figures S2 and S3).

Note that avg_dosage refers to cumulative modafinil dosage in mg divided by the duration of pregnancy in days. Thus, the effects reported in the tables above refer to a 1 mg increase in dosage, while in the main text 100 mg effects were reported for better readability. For separations by country, the reference is always France. All confidence intervals have a level of 95%.

Model for birth weight: all countries combined (Figure S2)

Coefficient tables and summary statistics for all cases combined (N=121), represented in Figure S2 by the black regression line.

term	estimate	std.error	statistic	p.value	conf.low	conf.high
(Intercept)	0.0544	0.126	0.432	0.667	-0.195	0.304
avg_dosage	-0.00275	0.000864	-3.19	0.00184	-0.00446	-0.00104

summary statistics	
r.squared	0.0786
adj.r.squared	0.0709
sigma	1.01
statistic	10.2
p.value	0.00184
df	1
logLik	-172
AIC	350
BIC	359
deviance	122
df.residual	119
nobs	121

Model for birth weight: full interaction by country (slope and intercept, Figure S2)

Coefficient tables and summary statistics for all countries separately, represented in Figure S2 by the colored regression lines.

term	estimate	std.error	statistic	p.value	conf.low	conf.high
(Intercept)	0.324	0.211	1.54	0.127	-0.0936	0.741
avg_dosage	-0.0043	0.00117	-3.67	0.000373	-0.00662	-0.00198
country Germany	-0.913	0.434	-2.11	0.0375	-1.77	-0.0536
country Israel	-0.746	0.431	-1.73	0.0867	-1.6	0.109
country other	-0.111	0.308	-0.36	0.72	-0.721	0.499
country Spain	-0.808	0.556	-1.46	0.148	-1.91	0.292
avg_dosage:country Germany	0.00774	0.00357	2.16	0.0326	0.000654	0.0148
avg_dosage:country Israel	0.00763	0.00562	1.36	0.178	-0.00351	0.0188
avg_dosage:country other	0.00158	0.00203	0.78	0.437	-0.00243	0.0056
avg_dosage:country Spain	0.00245	0.00617	0.398	0.692	-0.00977	0.0147

summary statistics	
r.squared	0.155
adj.r.squared	0.0863
sigma	1
statistic	2.26
p.value	0.0232
df	9
logLik	-167
AIC	356
BIC	387
deviance	112
df.residual	111
nobs	121

Model for birth weight: interaction by country on slope, but not on intercept (Figure S3)

Coefficient tables and summary statistics for the regression lines in Figure S3. In the model with full interaction (Figure S2), the country-specific intercepts, i.e. the estimated SDS means for BW at a modafinil dosage of 0 mg, differ by almost 1 SD. This difference is quite large and therefore likely to be an overestimate, having a substantial effect on the estimated slopes. While no country-specific differences in intercept are also unlikely, this second model allows the reader to consider the spectrum between these two extremes.

term	estimate	std.error	statistic	p.value	conf.low	conf.high
(Intercept)	0.0434	0.131	0.331	0.741	-0.216	0.303
avg_dosage	-0.00314	0.000962	-3.26	0.00145	-0.00505	-0.00123
avg_dosage:country Germany	0.00246	0.00249	0.986	0.326	-0.00248	0.0074
avg_dosage:country Israel	0.00169	0.00413	0.41	0.683	-0.00649	0.00988
avg_dosage:country other	0.0012	0.00153	0.787	0.433	-0.00183	0.00424
avg_dosage:country Spain	-0.00321	0.00436	-0.737	0.463	-0.0118	0.00542

summary statistics	
r.squared	0.0961
adj.r.squared	0.0568
sigma	1.02
statistic	2.44
p.value	0.0381
df	5
logLik	-171
AIC	356
BIC	376
deviance	120
df.residual	115
nobs	121

Figure S4

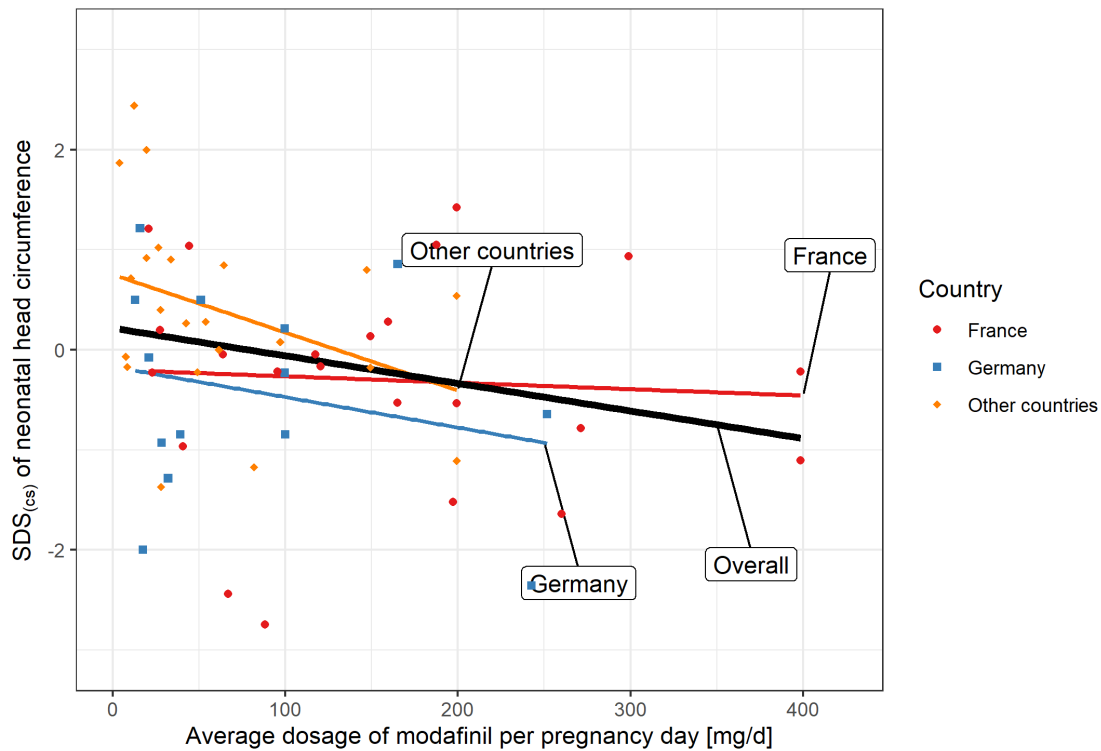


Figure S4. Potential dose-dependent effects of modafinil on neonatal head circumference (HC): Country-specific and overall correlations in a linear regression model. For statistical details of this model, see Table S7 (presented below Figure S5). The **black line** represents the regression line for all cases combined (N=59). Other countries refers to all countries with less than ten observations for HC, i.e. Italy, Japan, Spain, Switzerland, Turkey and United Kingdom. SDS(cs): Standard deviation scores based on country-specific reference charts and taking into account neonatal sex and GW at delivery. The linear model to evaluate interactions between intercept and country as well as slope and country finds only small, non-significant differences in the intercept and slope of the different countries. Taking into account all countries and assuming an average dosage per pregnancy day of zero (i.e. no modafinil exposure), our linear model obtained an SDS of 0.22 (95%CI, -0.19 to 0.62). In an additional model, we eliminated the impact of sample-specific intercept differences between countries by using the same intercept for each country (see Figure S5).

Figure S5

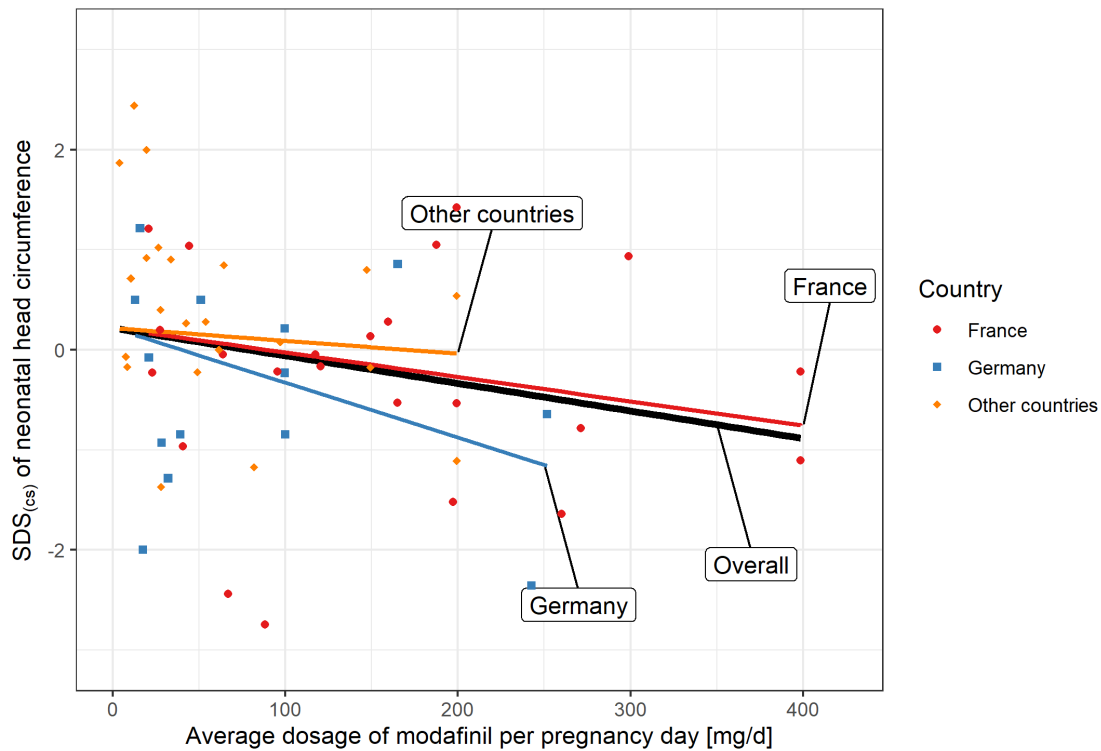


Figure S5: Potential dose-dependent effects of modafinil on neonatal head circumference (HC). Additional linear regression model to eliminate the impact of sample-specific intercept differences between countries. The **black line** represents the regression line for all cases combined (N=59). Using a common intercept for all countries results in even smaller differences in the slope of the different countries than the original model (Figure S4). For statistical details of this model, see Table S7 (presented below this Figure). Other countries refers to all countries with less than ten observations for HC, i.e. Italy, Japan, Spain, Switzerland, Turkey and United Kingdom. SDS(cs): Standard deviation scores based on country-specific reference charts and taking into account neonatal sex and GW at delivery.

Table S7. Coefficient tables and summary statistics for the exploratory linear models of potential dose-dependent effects on neonatal head circumference (for Figures S4 and S5).

Note that avg_dosage refers to cumulative modafinil dosage in mg divided by the duration of pregnancy in days. Thus, the effects reported in the tables refer to a 1 mg increase in dosage, while in the main text 100 mg effects were reported for better readability. For separations by country, the reference is always France. All confidence intervals have a level of 95%.

Model for neonatal HC: all countries combined (Figure S4)

Coefficient tables and summary statistics for all cases combined (N=59), represented in Figure S4 by the black regression line.

term	estimate	std.error	statistic	p.value	conf.low	conf.high
(Intercept)	0.217	0.203	1.07	0.29	-0.19	0.623
avg_dosage	-0.00276	0.00143	-1.92	0.0595	-0.00563	0.000114

summary statistics	
r.squared	0.0609
adj.r.squared	0.0444
sigma	1.06
statistic	3.7
p.value	0.0595
df	1
logLik	-86.2
AIC	178
BIC	185
deviance	64.2
df.residual	57
nobs	59

Model for neonatal HC: full interaction by country (slope and intercept, Figure S4)

Coefficient tables and summary statistics for all countries separately, represented in Figure S4 by the colored regression lines.

term	estimate	std.error	statistic	p.value	conf.low	conf.high
(Intercept)	-0.201	0.378	-0.531	0.598	-0.958	0.557
avg_dosage	-0.000643	0.00198	-0.325	0.747	-0.00462	0.00333
country Germany	0.0327	0.554	0.059	0.953	-1.08	1.14
country other	0.954	0.494	1.93	0.0587	-0.0364	1.94
avg_dosage:country Germany	-0.0024	0.00403	-0.595	0.554	-0.0105	0.00568
avg_dosage:country other	-0.00515	0.00423	-1.22	0.229	-0.0136	0.00333

summary statistics	
r.squared	0.166
adj.r.squared	0.0869
sigma	1.04
statistic	2.1

summary statistics	
p.value	0.0792
df	5
logLik	-82.7
AIC	179
BIC	194
deviance	57.1
df.residual	53
nobs	59

Model for neonatal HC: interaction by country on slope, but not on intercept (Figure S5)

Coefficient tables and summary statistics for the regression lines in Figure S5. In the model with full interaction (Figure S4), the country-specific intercepts, i.e. the estimated SDS means for neonatal HC at a modafinil dosage of 0 mg, differ by almost 1 SD. This difference is quite large and therefore likely to be an overestimate, having a substantial effect on the estimated slopes. While no country-specific differences in intercept are also unlikely, this second model allows the reader to consider the spectrum between these two extremes.

term	estimate	std.error	statistic	p.value	conf.low	conf.high
(Intercept)	0.218	0.214	1.02	0.313	-0.211	0.647
avg_dosage	-0.00244	0.00148	-1.65	0.106	-0.00542	0.000533
avg_dosage:country Germany	-0.00303	0.00276	-1.1	0.277	-0.00857	0.0025
avg_dosage:country other	0.00117	0.00304	0.384	0.703	-0.00493	0.00727

summary statistics	
r.squared	0.0874
adj.r.squared	0.0376
sigma	1.07
statistic	1.76
p.value	0.166
df	3
logLik	-85.4
AIC	181
BIC	191
deviance	62.4
df.residual	55
nobs	59

Figure S6

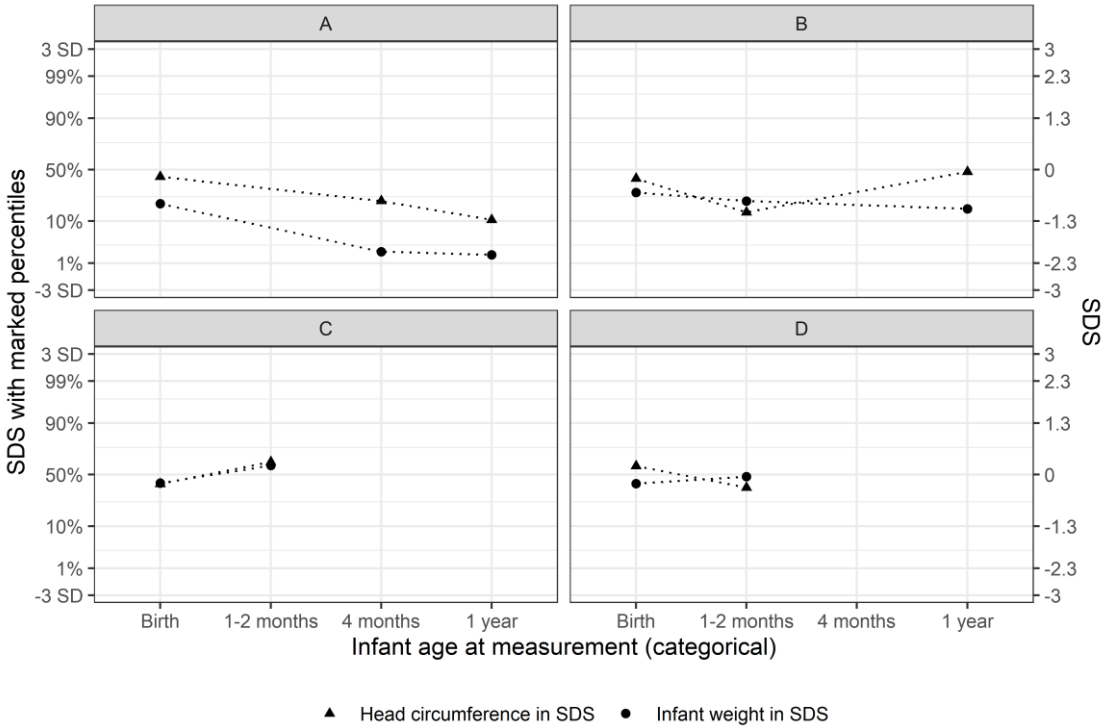


Figure S6. Postnatal growth curves for weight and head circumference (HC). Postnatal growth of four children from the United States [A], Australia [B] and Germany [C and D], none of them with MCA. Weight and HC in SDS (standard deviation scores) with marked percentiles, infant age in categories. For child A, percentile ranges of infant weight and HC were continuously decreasing with infant age: Over the course of the first year of life, the percentile for weight decreased from the 20th to below the 2nd percentile, and for HC from just below median to the 10th percentile. Additionally, developmental delay was reported. For the other three children, no overall trend of decreasing percentile ranges was identified.