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Consanguinity and pregnancy outcomes in a multi-ethnic, metropolitan European population

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2 **Consanguinity and pregnancy outcomes in a multi-ethnic, metropolitan**
3 **European population**

4 **Running head:** Consanguinity and prenatal health

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31 WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

32 Numerous studies of postnatal cohorts show that consanguineous couples have an increased
33 risk of major anomalies in their offspring. Up to now, no comprehensive study exists showing
34 that the risk of major congenital anomalies in the offspring of consanguineous couples is
35 higher than previously estimated if the prenatal situation is included

36

37 WHAT DOES THIS STUDY ADD?

38 Adjusted frequencies of major anomalies were 2.8% in non-consanguineous, 6.1% in
39 consanguineous couples (8.5% in first cousin progeny, 3.9% in beyond first cousin).
40 Applying a further adjustment for the significantly different frequencies of trisomic
41 pregnancies (consanguineous: n = 1, non-consanguineous: n = 262), the overall risks were
42 2.0% and 5.9% respectively, i.e. a 3.9% excess risk attributable to consanguinity, 6.1% at
43 first cousin level, 1.9% beyond first cousin level.

44

45

46 Statement: Originality of publication

47 The paper is submitted nowhere else.

48

49 Statement: Ethics

50 The data are anonymized retrospective evaluations of normal clinical treatment. Institutional
51 or national ethical committee approval is therefore not required.

52

53 **OBJECTIVE:** Aim of the present study was to assess the risk of major anomalies in the
54 offspring of consanguineous couples, including data of the prenatal situation.

55 **METHODS:** Over 20 years (1993-2012), 35,391 fetuses were examined by prenatal
56 sonography. In 675 cases (1.9%) parents were consanguineous, with 307 couples (45.5%)
57 related as first cousins, 368 couples (54.5%) beyond first cousins,. Detailed information was
58 retrieved on 31,710 (89.6%) fetuses, (consanguineous 568: 1.8%).

59 **RESULTS:** Overall prevalence of major anomalies among fetuses with non-consanguineous
60 parents was 2.9% (consanguineous: 10.9%: first cousins 12.4%, beyond first cousins 6.5%).
61 Adjusting the overall numbers for cases having been referred because of a previous index
62 case, the prevalences were 2.8% (non-consanguineous) and 6.1% (consanguineous) (first
63 cousin 8.5%, beyond first cousin 3.9%). Further adjustment for differential rates of trisomic
64 pregnancies indicated 2.0%/5.9% congenital anomalies (non-consanguineous/consanguineous
65 groups), i.e. a consanguinity-associated excess of 3.9%, 6.1% in first cousin progeny and
66 1.9% beyond first cousin.

67 **CONCLUSIONS:** The prevalence of major fetal anomalies associated with consanguinity is
68 higher than in evaluations based only on postnatal life. It is important that this information is
69 made available in genetic counselling programmes, especially in multi-ethnic and multi-
70 religious communities, to enable couples to make informed decisions.

71

72 Introduction

73 Marriages between couples related as second cousins or closer are common in many societies
74 and it is estimated that at least 10.4% of the current world population of 7.2 billion people are
75 consanguineous, with first cousin marriages by far the most prevalent type of intra-familial
76 union.¹⁻³ The frequency of consanguineous marriage is especially high in South, Central and
77 West Asia, and in North and sub-Saharan Africa², and in countries such as Pakistan first
78 cousin marriages alone account for >50% of all marital unions.⁴ Given the presence of large
79 Asian and African immigrant communities in Europe, North America, and Oceania⁵⁻¹⁴,
80 consanguineous pregnancies are now routinely encountered in many antenatal clinics in
81 Western countries, which has resulted in heightened interest in the possible association
82 between consanguinity and adverse pregnancy outcomes.

83 Data from epidemiological studies evaluating health outcomes have consistently shown that
84 the offspring of consanguineous parents may be at increased risk of morbidity and death in
85 the first years of life, due to the expression of detrimental recessive genes co-inherited from a
86 common ancestor.^{1,3,15-19} A recent multi-population meta-analysis indicated a mean excess
87 infant death rate of 1.3% in the progeny of first cousins, with a total excess pre-reproductive
88 mortality at first cousin level of 3.7%.² When compared with non-consanguineous offspring,
89 first cousin progeny had a 4.4% mean excess risk of a major congenital defect (median excess
90 risk = 3.3%).²

91 To date, information on the effects of consanguinity on fetal well-being have been very
92 limited, with few representative data available on fetal losses or on the prevalence of major
93 congenital anomalies. Since a proportion of pregnancies with major anomalies may end in
94 intrauterine death, or in medical termination, estimates of fetal defects based only on
95 postnatal data may be misleading. The present detailed study was therefore undertaken to
96 provide information on two important topics:

97 1) The frequency of fetuses with consanguineous parentage in a major European metropolitan
98 population;

99 2) The comparative frequency of major anomalies resulting in intrauterine or neonatal
100 death (IUD/NND), medical termination of pregnancy (MTO), and neonatal survival in the
101 offspring of consanguineous and non-consanguineous parents.

102

103 **Patients and Methods**

104 The study was based on sonographic examinations (some undertaken in combination with
105 sonographically guided invasive procedures) conducted in a specialist reference centre in
106 Berlin, the capital of Germany over a 20-year period (January 2, 1993 to December 30,
107 2012). A total of 35,391 fetuses in 34,256 pregnancies with a gestational age of more than 10
108 weeks underwent prenatal examination, including 953 sets of twins, 73 sets of triplets and 12
109 sets of quadruplets.

110 Various reasons for referral were given, including a positive family history; suspicion of a
111 malformation raised by a referring colleague; problems in sonographic depiction, for
112 example, because of maternal obesity; or concern of the pregnant woman with regard to
113 possible fetal anomalies and her wish, and that of the referring physician, to exclude fetal
114 anomalies wherever possible. However, in the latter instance the German legal guidelines on
115 pregnancy surveillance curtail the right of a woman to be referred for a detailed scan only
116 where there is suspicion of an anomaly.

117 All ultrasound examinations were performed by a single operator (RB), and the sonographic
118 instruments used were, respectively, an Acuson 128XP10, a Siemens Acuson Sequoia, and a
119 GE Voluson E8. In addition to the ultrasound examinations, patients' histories were assessed
120 by questionnaires as well as personal interviews.

121 The ultrasound examinations were conducted between 10+0 and 42+0 weeks gestation
122 (median 21+2 weeks), with 11,108 fetuses examined between 10+0 and 13+6 weeks, i.e. at
123 the first trimester anomaly scan, and 16,814 fetuses examined between 20+0 and 23+6
124 weeks, i.e. at the second trimester anomaly scan. A total of 4,771 fetuses were examined
125 between 14+0 and 19+6 weeks and 2,698 fetuses between 24+0 and 41+3 weeks. According
126 to the German system of perinatal care, all newborns were examined by a midwife

127 immediately after birth and by a paediatrician between days five and ten of life. Reports on
128 the health status of the newborns, either provided by mothers or in medical reports, were
129 based on the results of these mandatory examinations. A major anomaly was defined as a
130 defect present during pregnancy after 10 weeks gestation that, in the absence of treatment,
131 either was incompatible with life or would lead to a severe handicap and would be detectable
132 during the paediatric examination at five to 10 postnatal days.^{20,21}

133 As part of a standardized form distributed during the explanatory talk preceding ultrasound
134 examination, each patient was asked during the first prenatal interview whether she and her
135 partner were biological relatives, and if so the nature of their relationship, i.e. categorized as
136 first cousin, equivalent to a coefficient of inbreeding, $F = 0.0625$, or related to a lesser
137 degree, $F < 0.0625$. All patients also were requested to complete and return a feedback form
138 after delivery, containing information on their pregnancy, the birth, and the health of their
139 newborn.

140 Feedback on the fetal outcome was retrieved for 31,710 (89.6%) of the 35,391 cases,
141 representing 568/675 (84.1%) of the consanguineous and 31,141/34,716 (89.7%) of the non-
142 consanguineous cases respectively (Table 2). In 15,730 cases (consanguineous, $n = 191$) the
143 form was returned by the patient, and in 15,411 cases (consanguineous, $n = 377$) by
144 contacting the patient or, especially in cases with an adverse pregnancy outcome, via the
145 referring physician or the hospital where the child had been delivered or the pregnancy had
146 been terminated. The information on the health status of the fetus/newborn contained all
147 ultrasound results during the pregnancy as well as post-partum information retrieved by the
148 second routine examination of the newborn performed between day 5 and 10 of neonatal life.

149 A majority of the ultrasound examinations was undertaken for screening purposes.

150 In patients with a congenital anomaly, the frequency referred because of the medical history
151 of an index child with an autosomal recessive disorder in the consanguineous group was
152 much higher (29 of 62: 46,8%) than in the non-consanguineous group (10 of 893: 1.1%)
153 (Table 3, Suppl. Table 5)..

154 Data on ethnicity and maternal age were available for all 675 consanguineous cases
155 and for 34,526 (99.5%) of the non-consanguineous fetuses (Table 1). Patients were classified
156 into five major groups:

- 157 1. European, predominantly German, but also parents from other European countries and of
158 European ancestry, including North and South America, Russia and Australia;
- 159 2. Turkish, i.e. parents from Turkey, which may include parents of Kurdish ethnicity;
- 160 3. Eastern Mediterranean, i.e. from Iran, Iraq, Israel, Kuwait, Lebanon, Oman, Palestine,
161 Syria, Saudi Arabia, and Yemen; also Egypt and the Maghreb states Algeria, Libya,
162 Morocco, Tunisia, as well as Pakistan and Sudan;
- 163 4. African, mainly sub-Saharan, and
- 164 5. South, Southeast and East Asian, i.e. Bangladesh, China, India, Indonesia, Nepal, The
165 Philippines.

166 The data on an association between consanguinity and a major fetal anomaly were divided
167 into three categories. A causative association between consanguinity and fetal or neonatal
168 disease was assessed as:

- 169 1. **Probable:** if i) the disease was rare and had a well described autosomal recessive mode of
170 inheritance, and/or, ii) there were several identical anomalies affecting fetuses previously
171 conceived by a woman (or in the pregnancies of close biological relatives), with a suspected
172 but as yet unproven autosomal recessive mode of inheritance;
- 173 2. **Possible:** in cases of anomalies that may occur as autosomal recessive diseases but where
174 the mode of inheritance was unclear and no repeat case was known;
- 175 3. **Improbable:** in cases known not to have an autosomal recessive mode of inheritance, and
176 in cases with numerical or structural chromosomal abnormalities.

177 Statistical analysis

178 The statistical analysis was performed using the SAS®9.2 program (SAS Institute Inc., Cary,
179 North Carolina, USA). Summary statistics are presented as counts and percentages in the case
180 of categorically scaled measures and as mean, median, standard deviation and range in the
181 case of continuously scaled variables, with the fetus or the mother as the unit of analysis.

182 Multivariable Poisson regression was undertaken to investigate the effect of
183 consanguinity on the occurrence of anomalies, with the analysis adjusted for maternal age,
184 ethnicity and the birth number (1st pregnancy: y/n). The latter adjustment was performed in
185 order to address a possible referral bias. Pregnancy was the unit within these analyses; in the
186 case of multiple pregnancies the fetus with worst birth outcome was used in the analysis. As a
187 further sensitivity analysis to address missing information on fetal outcome, the Poisson
188 regression was repeated by applying multiple imputation²² of missing information (SAS
189 procedures PROC MI, PROC MIANALYZE, 20 imputation cycles), under the assumption
190 that missing outcome information (MAR) could be explained by consanguinity, ethnicity,
191 maternal age and first pregnancy y/n ("missing at random assumption" (MAR)²³).

192

193 **Results**

194 Of the total 35,391 fetuses examined 676 (1.9%) were the offspring of consanguineous
195 parents. In one of these cases the pregnancy was conceived by egg donation and so it was
196 categorized as genetically non-consanguineous, resulting in 675 fetuses conceived by
197 consanguineous parents (Table 1). Within this group, the parents of 307/675 (45.5%) fetuses
198 were first cousins, with an established outcome in 275 cases; the parents of 368/675 (54.5%)
199 fetuses were related beyond first cousin, with an established outcome in 293 cases.

200 The frequency of parental consanguinity varied significantly according to the ethnicity of the
201 mothers, from just 0.07% in European, predominantly German couples, to 21.8%
202 consanguinity in couples of Eastern Mediterranean/Maghreb ethnicity who formed 33.6% of
203 the total consanguinity group, and 17.2% in women of Turkish origin who comprised 61.5%
204 of all consanguineous cases (Table 1).

205 The overall frequency of major anomalies was 893/31,141 (2.9%) in the non-consanguineous
206 group, 22 of them with a well known autosomal-recessive background (Table 3, Suppl. Table
207 5). In the consanguineous group, the frequency of major anomalies was 62/568 (10.9%). As
208 previously noted, in the consanguineous group 29/62 cases had been referred because of a
209 preceding index case, by comparison with 10/893 non-consanguineous cases (Suppl. Table

210 5). Adjusting for the pregnancies with preceding index cases and analysing in terms
211 of the level of parental consanguinity the percentages of congenital anomalies diagnosed
212 were: all consanguineous 6.1% (33 of 539), first cousin 8.5% (22 of 259), beyond first cousin
213 3.9% (11 of 280), and non-consanguineous 2.8% (883 of 31,131) (Tables 2, 3).

214 The frequency of anatomically complex diseases also was higher in the total consanguineous
215 (3.7%) than in the non-consanguineous (1.5%) group. Conversely, while 0.7% of the
216 consanguineous group was diagnosed with chromosomal anomalies with 177 cases of
217 trisomy 21, 56 cases of trisomy 18 and 29 cases of trisomy 13., the prevalence of
218 chromosomal anomalies in the non-consanguineous group was 1.2% (Table 2) with 1 case of
219 trisomy 21 and no cases of trisomy 13 or 18.

220 Additional investigative procedures, including chorionic villous sampling, amniocentesis and
221 fetal blood sampling, were less frequently undertaken in the pregnancies of women in a
222 consanguineous relationship (7.0%) than non-consanguineous women (11.7%). A similar
223 pattern emerged in the cases where a major anomaly was suspected, with 14.5% of
224 consanguineous cases as opposed to 30.7% of non-consanguineous pregnancies further
225 investigated (Suppl. Table 1).

226 Detailed information on the 62 cases of major anomalies considered to be probably, possibly,
227 or improbably associated with parental consanguinity is presented in Tables 3 and 4. In cases
228 1-37 (59.7%), 21 of whom had first cousin parents and 16 with parents related beyond first
229 cousins, a causal relationship of the disease with consanguinity was assessed as probable, e.g.
230 glycogenosis or SMA Werdnig-Hoffmann (Table 3). In cases 38-56 (30.6%), 11 of whom
231 had first cousin parents and 8 with parents related beyond first cousins, an association
232 between the major anomaly and consanguinity was possible but could not be proven, e.g.
233 hydrops of unknown aetiology (Table 4). In cases 57-62 (9.7%), all of whose parents were
234 first cousins, there was no obvious association between the major anomaly and parental
235 consanguinity, e.g. Klinefelter syndrome (Table 4). In 10/37 cases listed in Table 3 a
236 diagnosis was possible by molecular diagnostics following an invasive procedure; in 3 further

10

237 cases of this group diagnosis would have been possible but was declined by the
238 pregnant woman.

239 Intra-uterine death occurred in 9.7% of the consanguineous fetuses versus 4.9% of the non-
240 consanguineous pregnancies, and the corresponding data on medical terminations of
241 pregnancy were 50.0% and 60.9% respectively. Nine of 62 (14.5%) fetuses of
242 consanguineous progeny with major anomalies died within the first year of life, 3 within the
243 first week. Detailed information on the time and mode of detection as well as time and mode
244 of the demise (unless the newborn survived) of the fetus/newborn are given in columns 6 and
245 9 of table 3 and columns 5 and 8 of table 4.

246 The results of adjusted, multivariable analyses (without and with multiple imputation of
247 missing information) are presented as Supplementary Results. A ratio of abnormalities
248 Cons/P/NConsP of 3.00 (95% CI: 2.17 – 4.14) [multiple imputation: 3.00 (95% CI= 2.15 –
249 4.19)] was found. In the preparation of multiple imputation, all investigated variables were
250 identified as explanatory variables for missing information of outcome (Suppl. Table 1).

251

252 **Discussion**

253 To the best of our knowledge this is the first comprehensive study analysing the impact of
254 consanguinity on the frequency of congenital anomalies which includes comprehensive data
255 on prenatal life from week 10 onwards. Besides the integration of prenatal data, a major
256 advantage of the evaluation is the size of the study group which gives a representative picture
257 of the diagnostic situation faced.

258 The overall frequency of fetuses with consanguineous parentage in our study population was
259 low (1.9%) in comparison to the many countries where 20-50+% of all marriages are
260 consanguineous (www.consang.net).^{2,3} Consanguinity was strongly associated with ethnicity:
261 consanguineous relationships were most common among couples of Turkish or Eastern
262 Mediterranean/Maghreb origin, with 95.1% of all consanguineous fetuses studied conceived
263 by couples from these backgrounds.

264 The investigation was based on retrospective data gained as part of the daily routine of a
265 specialist prenatal practice over 20 years. When such observational data are analysed possible
266 biases influencing the result have to be considered. First, one could assume that the women
267 undergoing prenatal diagnosis following their first pregnancy might differ from those women
268 who visited the practice during their first pregnancy (1st pregnancy y/n). We therefore
269 undertook a multivariable analysis investigating the effect of consanguinity on the occurrence
270 of anomalies and adjusted the analysis for this factor (together with age and ethnicity). The
271 related IDR (1st pregnancy y/n) was 1.03 (95%-CI: 0.90 - 1.19, $p = 0.62$), indicating that such
272 bias was negligible (Suppl. Table 1). Second, the feedback rate of pregnancies was lower in
273 the consanguineous (84.1%) than in the non-consanguineous (89.6%) group, which might
274 also influence the result. We therefore used multiple imputation²², assuming that the rate of
275 missing information on the occurrence of an anomaly can completely be explained by
276 variables (consanguinity, age, ethnicity, first pregnancy (y/n)) investigated in the study (MAR
277 assumption).²³ Although all variables could potentially influence the rate of missing
278 information, the overall result was almost identical: (MI analysis: IDR (cons y/n) = 3.00

279 (95%-CI: 2.15 - 4.19, $p < 0.0001$) vs. complete case analysis: 3.00 (95%CI: 2.17 -
280 4.14, $p = 0.0001$) (Suppl. Table 1).

281 The analysis thus shows that with respect to these possible variables the original analysis of
282 10.9% vs. 2.9% (ratio 3.8) congenital anomalies in the consanguineous and non-
283 consanguineous groups moderately overestimated the apparent influence of consanguinity on
284 the occurrence of anomalies, i.e. consanguinity significantly influences the occurrence of
285 anomalies independently of other factors. It therefore is appropriate to present further detailed
286 analyses simply as counts and percentages.

287 In overall terms, Table 3 lists 8 cases with a congenital anomaly probably associated with
288 consanguinity because of an established autosomal recessive inheritance but without a
289 preceding index child. Table 4 lists 19 cases possibly related to consanguinity and 6 cases
290 probably not related to consanguinity.

291 The degree of consanguinity had important influence on the frequency of major anomalies:
292 looking at all consanguineous cases, the frequency of 6.1% could be differentiated into a
293 subgroup of first cousin relations with a frequency of major anomalies of 8.5% and a
294 subgroup beyond first cousin with a frequency of 3.9% respectively.

295 Having adjusted for previously diagnosed index cases and assuming similar background risks
296 in the consanguineous and non-consanguineous cases, congenital anomaly rates of 33/539
297 (6.1%) and 883/31,131 (2.8%) are indicated in the cases with consanguineous and non-
298 consanguineous parentage respectively.

299 Consanguineous women were, however, significantly younger than non-consanguineous
300 women (Table 1) resulting in a differential age-dependent frequency of trisomies. In the non-
301 consanguineous group there were 262 trisomy cases (T21: $n = 177$; T18: $n = 56$; T13: $n =$
302 29), i.e. a frequency of 262/893 (29.3%) major anomalies. As previously noted, this group of
303 non-consanguineous fetuses also comprised 22 cases with an established autosomal recessive
304 mode of inheritance (Suppl. Table 5), 10 of whom had a preceding index case.

305 The background frequency of the non-consanguineous group corrected for autosomal
306 recessive cases with a preceding index case and trisomies results in an adjusted frequency of

307 $[(893-10-262)/(31,141-10-262)] = 2.0\%$. By comparison, in the consanguineous group,
308 besides the autosomal recessive cases with a preceding index patient there was a single case
309 of trisomy 21 resulting in an adjusted major anomaly frequency of $[(62-29-1)/(568-29-1)] =$
310 5.9% . The overall excess consanguinity-associated prevalence of congenital anomalies in the
311 combined offspring of first cousin and beyond first cousin parents is therefore $5.9\%-2.0\% =$
312 3.9% : 6.1% ($100 \times (22-1/275-1-16)\% - 2\%$) at first cousin level and 1.9% ($100 \times (11/293-13)\%$ -
313 2%) beyond first cousin level. By comparison, meta-analyses of multi-national data have
314 indicated a 0.5% increase in stillbirths and a 1.25% increase in infant deaths among the
315 progeny of first cousin parents².

316 Where the fetus was diagnosed with a major congenital anomaly there was a high prevalence
317 of medical termination of pregnancy in both the consanguineous (50.0%) and non-
318 consanguineous pregnancies (60.9%). The high rate of medical terminations of affected
319 fetuses conceived by consanguineous couples of Turkish or Eastern Mediterranean origin
320 (Tables 3 and 4) appears to be indicative of more permissive attitudes towards MTOP within
321 some Islamic communities.²⁴

322 As summarized in Table 5, in assessing the influence of parental consanguinity on congenital
323 anomalies it is important that prenatal outcomes and early neonatal deaths are fully
324 considered. In the study group, $307/955$ (32.2%) fetuses with major anomalies survived the
325 first neonatal week, with quite similar survival outcomes in the fetuses of consanguineous
326 (35.5%) and non-consanguineous (31.9%) parentage (Table 5). From the perspective of a
327 paediatrician, possibly unaware of MTOP, IUD or NND of the child within the first week, the
328 frequency of major anomalies in fetuses with consanguineous parentage, including those
329 referred following an index case, would have been estimated as 3.9% ($22/568$). However this
330 mode of calculation significantly under-estimates the overall fetal (and neonatal) problems
331 that may be associated with consanguineous pregnancies, even in populations where
332 consanguineous marriage is quite rare. Appropriate allowance for the influence of
333 consanguineous parentage becomes all the more important in multi-ethnic populations where

14

334 a significant proportion of pregnancies are between close biological kin and/or
335 contracted within restricted community marriage pools.^{2,3,25,26}

336 With the increasing capacity to maintain fetal life from the second trimester onwards, and to
337 rapidly identify rare inherited disorders by methods such as high-level ultrasound²⁷, whole
338 genome sequencing in the prenatal period²⁸ and in neonates²⁹, and diagnostic whole exome
339 sequencing³⁰, comprehensive pre- and postnatal procedures need to be devised for adverse
340 consanguinity-associated health outcomes.³¹ At the same time, it is important that the
341 information derived be incorporated into genetic counselling programmes that both
342 acknowledge and respect the religious and cultural beliefs of couples and their communities,
343 and the perceived social benefits of intra-familial marriage.^{3,32,33} The present study impinges
344 on a potentially very sensitive issue and for this reason the data analysis has been conducted
345 with no attempt to draw any form of moral inference from the results. It therefore is
346 important that the information derived is not assessed outside a medical context or used as a
347 basis for cultural or political discourse.

348

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- 425

426 **Tables**

427

Ethnic background	Consanguineous	Non-consanguineous	All	Consanguinity (%)	Maternal age by ethnicity, mean \pm SD, range
European	22 (3.3%)	31,042 (89.9%)	31,064 (88.3%)	0.07%	31.9 \pm 5.2 15-50 years
Turkish	415 (61.5%)	1,994 (5.8%)	2,409 (6.9%)	17.2%	28.9 \pm 5.6 15-47 years
Eastern Mediterranean / Maghreb	227 (33.6%)	817 (2.4%)	1,044 (3.0%)	21.8%	29.5 \pm 6.4 16-44 years
African	0	112 (0.3%)	112 (0.3%)	0%	29.9 \pm 5.2 18-41 years
Asian	11 (1.6%)	561 (1.6%)	572 (1.6%)	1.9%	31.6 \pm 5.2 15-47 years
Maternal age mean \pm SD, range	28.0 \pm 5.6* 16-44 years	31.7 \pm 5.3 15-50 years			31.6 \pm 5.4, 15-50 years

428

429

430 **Table 1:** Consanguinity, ethnicity and maternal age in mothers of 35,201 fetuses, 1993-2011.

431 Information was available on maternal age and ethnicity in all 675 fetuses with
 432 consanguineous parents but was missing in 190 of the non-consanguineous group. Women in
 433 consanguineous relationships were significantly younger than in non-consanguineous
 434 relationships (*t-test, $p < 0.0001$).

435 (Information was available on the ethnic background of all 675 consanguineous fetuses and
 436 on 99.5% of 34,716 fetuses with non-consanguineous parentage.)

437

438

Disorders diagnosed	Consan- guineous	%	Non- consan- guineous	%	All cases	%
Total cases	675	100%	34,716	100%	35,391	100%
Information on fetal outcome missing	107	15.9%	3,575	10.3%	3,682	10.4%
Information on fetal outcome available	568	84.1%	31,141	89.7%	31,710	89.6%
No disorder	504		30,248		30,755	
All congenital disorders	62	10.9%	893	2.9%	955	3.0%
<i>Single gene defects</i>	37	6.51%	40	0.13%	77	0.24%
Autosomal dominant	0		15	0.05%	15	0.05%
Autosomal recessive	37	6.51%*	22	0.07%	59	0.19%
X-linked recessive	0		3	0.01%	3	0.01%
<i>All chromosomal aberrations</i>	4	0.70%†	367	1.18%	371	1.17%
Numerical chromosomal aberrations	2	0.35%	322	1.03%	324	1.02%
non-gonosomal	1	0.18%	280	0.90%	281	0.89%
gonosomal	1	0.18%	42	0.13%	43	0.14%
Structural chromosomal aberrations	1	0.18%	23	0.07%	24	0.08%
Mosaicism	1	0.18%	22	0.07%	23	0.07%
Molecular genetic disorders	0		5	0.02%	5	0.02%
<i>Anatomically complex disorders with unclear genetic background</i>	21	3.70%	481	1.54%	502	1.58%

440

441

442 **Table 2:** Frequencies and patterns of inheritance of major congenital disorders in443 consanguineous and non-consanguineous pregnancies. Chi²-tests, †p = 0.23, *p < 0.0001

444

445

No	DOC	Diagnosis	M.o.i.	Fet aff. no	Mode/time of detection	Karyotype	US vis	Pregnancy outcome
First cousin cases with a probable causal relation to consanguinity ... with a positive history								
1	1C	<i>Arthrogyroposis</i>	AR/Rep	2	US 32 wks			+ NND 6 wks
2	1C	<i>Arthrogyroposis</i>	AR/Rep	3	US 29 wks			+ NND 3 days
3	1C	Hydrops of unclear origin	Rep	2	US 13 wks			+ MTOP 19 wks
4	1C	Hydrops of unclear origin*	Rep	2	US 28 wks			+ IUD 30 wks
5	1C	Mitochondriopathy	AR/Rep	2	Diag den Postnatal			- Delivery NND 11 months
6	1C	Glycogenosis II (Pompe) **	AR/Rep	2	US 21 wks			+ Delivery
7	1C	Meckel-Gruber syndrome	AR	2	US 22 wks			+ MTOP 22 wks
8	1C	Multicystic kidney disease	AR/Rep	2	US 21 wks			+ NND 1 day
9	1C	Multiple pterygium syndrome	Rep	2	FBA + US 31 wks	46,XX		+ IUD 33 wks
10	1C	Multicystic kidney disease	AR/Rep	2	US 23 wks			+ MTOP 23 wks
11	1C	β -thalassaemia	AR/Rep	2	CVS 13 wks	46,XX		- MTOP 17 wks
12	1C	Galactosaemia	AR/Rep	2	CVS 12 wks	46,XY		- MTOP 15 wks
13	1C	Osteopetrosis	AR/Rep	2	CVS 12 wks	46,XY		- MTOP 13 wks
14	1C	Fanconi anaemia	AR/Rep	2	CVS 13 wks	46,XY		- MTOP 15 wks
15	1C	Micro-syndrome	AR/Rep	6	CVS 15 wks	46,XY		- MTOP 16 wks
16	1C	Mucopolysaccharidosis VI	AR	2+fc..	AC 16 wks	46,XX		- MTOP 22 wks
... without a positive history								
17	1C	Surfactant-b-deficiency	AR	1	Postnatal			- NND 2 wks
18	1C	Citrullinaemia	AR	1	Postnatal			- Delivery
19	1C	Meckel-Gruber syndrome	AR	1	US 12 wks			+ MTOP 13 wks
20	1C	Pierre-Robin-Syndrome	AR/Rep	1+f.c..	US 21 wks			+ Delivery
21	1C	Arthrogyroposis-renal-cholestasis-syndrome	AR	1	Diagnosis postnatally	AC 26 wks: 46,XX		Delivery NND 3 months
Cases beyond first cousins ... with a positive history								
22	<1C	Glycogenosis type II (Pompe)	AR/Rep	2	Diag den			- NND 7 months
23	<1C	<i>Glycogenosis type IV</i>	AR/Rep	2	Diag den			- NND 14 wks
24	<1C	<i>SMA Werdnig-Hoffmann</i>	AR/Rep	2	CVS 12 wks	46,XY		- MTOP 17 wks
25	<1C	<i>SMA Werdnig-Hoffmann</i>	AR/Rep	3	CVS 12 wks	46,XX		- MTOP 14 wks
26	<1C	SMA Werdnig-Hoffmann	AR/Rep	3	CVS 20 wks	46,XX		- MTOP 23 wks
27	<1C	<i>Adams-Oliver syndrome</i>	Rep	2	US 22 wks			+ MTOP 23 wks
28	<1C	<i>Adams-Oliver syndrome</i>	Rep	3	US 13 wks			+ MTOP 14 wks
29	<1C	Unclear syndrome with severe mental retardation	AR/Rep	2	Postnatal			- Delivery
30	<1C	Cockayne syndrome	AR/Rep	2	CVS 11 wks	46,XX		MTOP 19 wks
31	<1C	Microcephaly	Rep	2	US 37 wks			+ MTOP 37 wks
32	<1C	COFS	AR/Rep	2	US 31 wks			MTOP 31 wks
33	<1C	Unclear syndrome with cleft palate and skeletal dysplasia	AR/Rep	2	US 16 wks			+ MTOP 16 wks
34	<1C	Unclear skeletal dysplasia (OI?)	AR/Rep	2	US 26 wks			+ Delivery
... without a positive history (no preceding affected fetus/child)								
35	<1C	<i>Glycogenosis type IV</i>	AR/Rep	1	Postnatal			- NND 10 wks
36	<1C	Meckel-Gruber syndrome	AR	1	US 12 wks			+ MTOP 14 wks
37	<1C	Microcephaly	Rep	1+ fam.c.	US 21 wks			+ Delivery

448 **Table 3:** Overview of 37 cases (group A) showing a probable causal association of the
449 diagnosed anomaly with consanguinity.

450 Cases 4 and 6 were dizygotic twin pregnancies: *in case 4 one of the twins had intrauterine
451 demise at 34 weeks; **in case 6 first signs were seen at 21 weeks with diagnosis made
452 postnatally; in both cases the co-twins were normal. In the 8 cases of the 4 women printed in
453 bold (cases 1 and 2, cases 24 and 25, cases 27 and 28 and cases 35 and 23), the couples had
454 several children with an identical diagnosis in different pregnancies. Three of these 4 women
455 had a third affected fetus not listed here as Table 3 is based only on cases we examined in our
456 centre. Column 5 gives the number the previous affected fetuses of the couple investigated. In
457 9 of the 37 cases the anomaly occurred in the family for the first time.

458 DOC, degree of consanguinity; 1C, first cousin; <1C, beyond first cousin; mgt molecular
459 genetic test; Fet aff. No, fetus affected number; SMA, spinal muscular atrophy; COFS,
460 cerebro-oculo-facial syndrome, AR autosomal recessive; Rep, repetitive case; fam.c., familial
461 case; CVS, chorionic villous sampling; AC, amniocentesis, US, ultrasound; wks, weeks; Diag
462 den, diagnostics declined (pregnant woman did not accept invasive procedure); MTOP,
463 medical termination of pregnancy; IUD, intrauterine death; NND, neonatal death.

464

No.	DOC	Diagnosis	Fet aff no	Mode/time of detection	Karyotype	US vis	Pregnancy outcome
First cousin cases with a possible causal relation to consanguinity ... without a positive history							
38	1C	Hydrops of unclear origin	1	US 23 wks CVS+FBA	46,XX	+	IUD 30 wks
39	1C	Hydrops of unclear origin	1	US 11 wks CVS	46,XX	+	MTOP 14 wks
40	1C	Hydrops of unclear origin	1	US 19 wks		+	MTOP 22 wks
41	1C	Hydrops of unclear origin	1	US 20 wks		+	IUD 28 wks
42	1C	Hydrops of unclear origin	1	US 23 wks		+	IUD 23 wks
43	1C	Hydrops of unclear origin	1	US 16 wks		+	IUD 16 wks
44	1C	Hydrops, CHD	1	US 19 wks		+	MTOP 20 wks
45	1C	Heterotaxy syndrome	1	US 22 wks		+	MTOP 22 wks
46	1C	CHD: Taussig-Bing	1	US 22 wks		+	MTOP 23 wks
47	1C	Complex syndrome: Heart, CNS. Prior pregnancy hydrocephalus	1+1 diffe- rent	US 20 wks AC	46,XX	+	MTOP 23 wks
48	1C	Cleft lip and palate	1	US 21 wks AC	46,XY	+	Delivery
Cases beyond first cousin with a possible causal relation to consanguinity ... without a positive history							
49	<1C	Unclear syndrome with hydrothorax	1	US 14 wks CVS	46,XY	+	Delivery
50	<1C	Unclear syndrome, CHD, SUA, stigmata	1	US 22 wks		+	MTOP 22 wks
51	<1C	Complex anomaly of CNS	1	US 24 wks		+	Delivery
52	<1C	AV septal defect + CDH	1	US 22 wks		+	Delivery
53	<1C	Complex urogenital anomaly	1	US 21 wks		+	Delivery
54	<1C	Heterotaxy syndrome	1	US 22 wks		+	Delivery
55	<1C	CDH, history of 5 abortions	1	US 22 wks		+	NND day 1
56	<1C	Hydrocephalus; prior pregnancy: unclear syndrome, death 1 year	1+1 diffe- rent	US 16 wks AC	46,XX	+	MTOP 17 wks
First cousin cases with an improbable causal relation to consanguinity ... without a positive history							
57	1C	Klinefelter syndrome no clinical symptoms	1	US 17 wks AC	47,XXY	-	Delivery
58	1C	Paternal balanced translocation	1	US 13 wks CVS	5 p- (cri du chat)	-	MTOP 14 wks
59	1C	Bilateral renal agenesis	1	US 21 wks		+	MTOP 22 wks
60	1C	Down syndrome enlarged NT	1	US 13 wks CVS	47,XY +21	+	MTOP 18 wks
61	1C	Adactyly dig. 2-4 right hand	1	US 21 wks		+	Delivery
62	1C	Ebstein's anomaly chromosomal anomaly	1	US 21wks AC+FBA	mosaicism 46,XY/ 47,XY,+6	+	Delivery

468 **Table 4:** Overview of 19 cases with major anomalies (nos. 38-56, group B) showing a
469 possible causal association with consanguinity as well as 6 cases with major anomalies (nos.
470 57-62, group C) showing an improbable association with consanguinity. Column 4 gives the
471 number the previous affected fetuses of the couple investigated

472 DOC, degree of consanguinity; Fet aff no , fetus affected number; US vis, visibility by
473 ultrasound; wks, weeks; CVS, chorionic villous sampling; US, ultrasound; IUD, intrauterine
474 death; MTOP, termination of pregnancy for medical reasons; 1C, first cousin; <1C, beyond
475 first cousin; AV septal defect, atrio-ventricular septal defect; CDH, congenital diaphragmatic
476 hernia; CHD, congenital heart disease; CNS, central nervous system; SUA, single umbilical
477 artery; CVS, chorionic villous sampling; AC, amniocentesis; US, ultrasound; wks, weeks;
478 MTOP, medical termination of pregnancy; IUD, intrauterine death; NND, neonatal death;
479 NT, nuchal translucency.

480

		Consang.	Non-consang.	All cases
Prenatal	No. of congenital defects	62	893	955
	IUD	6 (9.7%)	44 (4.9%)†	50 (5.2%)
	MTOP	31 (50.0%)	544 (60.9%)	575 (60.2%)
	Survival to term	25 (40.3%)	305 (34.2%)	330 (34.6%)
Postnatal	NND within week 1	3 (4.8%)	20 (2.2%)	23 (2.4%)
	Postneonatal survival more than one week	22* (35.5%)	285 (31.9%)	307 (32.2%)

482

483

484 **Table 5:** Pregnancy outcomes of fetuses with major anomalies conceived by consanguineous
485 and non-consanguineous parents.

486 *Another six babies (nos.1, 5, 17, 22, 23, 35) died after the first week but within the first year
487 of life because of consanguinity-associated diseases.

488 †Chi²-test, p = 0.12

489