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Underestimation of Subfertility Among Relatives When Using a Family History: Taboo Bias

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ABSTRACT: Family history is widely used in clinical practice and research in order to study genetic aspects of disorders in general, and is recommended as a tool in the assessment of male subfertility. Unfortunately, little is known about the validity of this tool. In this survey, we sent questionnaires to 474 randomly selected men aged 25–40 years in order to collect data on subfertility among them and their relatives. A nonresponder study was also conducted in order to evaluate selection bias. A personal interview was also performed with some respondents in order to gauge how well the data corresponded with questionnaires that were returned. Two hundred forty-three men (51.3%) completed the questionnaire. The responders reported a significantly lower prevalence of subfertility among their relatives than among themselves. Among brothers, the reported prevalence was about 5 times lower (ie, 3.6%) than among responders (15.3%). The nonresponder study and personal interviews showed that these differences were not caused by a selective response to the survey or by the use of a questionnaire instead of a personal interview. We conclude that subfertility among relatives is severely underestimated through the use of family history, probably because of the taboo of discussing subfertility. Knowledge of subfertility may spread selectively within families, causing substantial misclassification. Therefore, researchers and clinicians should be aware that an inquiry of family history is likely to lead to underestimation of subfertility among relatives.

Key words: Epidemiology, misclassification, accuracy, fertility, genetics, familial occurrence.

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The prevalence of male subfertility in families and the accuracy of detecting fertility problems using a family history are unknown. Nevertheless, several authors suggest that a family history should be used in research and fertility practice (Lilford et al, 1994; Meschede et al, 1995; Tuerlings et al, 1997). Moreover, the use of a family history is recommended by the American Society for Reproductive Medicine (2002) in its guide for practical genetic evaluation and counseling for infertile couples.

Several studies have been carried out for the purpose of investigating the use of family history in medical decision-making for different heritable diseases (Dewey and Parker, 2000; Kulig et al, 2000; Sijmons et al, 2000; Aben et al, 2002). However, depending on the type of disease studied and the degree of family relatedness, family history is not always reliable. Verification of data using medical records of relatives may be necessary to prevent misclassification and to correctly interpret the family history (Kee et al, 1993). The use of a family history in the evaluation of fertility problems has not yet been evaluated.

We carried out a survey on familial occurrence of male subfertility to learn about the prevalence of subfertility among relatives of randomly sampled men. At the same time, we conducted a side study in order to investigate the use of a family history questionnaire as opposed to a personal interview.

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Methods

The study was approved by the institutional review board of University Medical Centre Nijmegen.

Questionnaire

Our study population consisted of 474 randomly sampled men aged 25–40 years living in Boxmeer, a typical Dutch municipality of average size and socioeconomic status, with its own industry, agriculture, and commerce. The sample was taken from the municipality basic administration system. Boxmeer is situated in southeast Netherlands and our university hospital is the tertiary medical center for the region. In the questionnaire we requested information on responders' medical and family history up to second-degree family members with a special focus on subfertility. In the accompanying letter, subfertility was defined as a lack of conception after at least 12 months of unprotected intercourse.

Responders and their relatives were classified into 1 of 4 categories: a) fertile, if they had established a pregnancy or had children without reporting subfertility; b) subfertile, if they reported subfertility according to the definition mentioned earlier; c) not at risk, if they did not report subfertility, or if they had no children because they were not in a heterosexual relationship,

Fertility status among probands and relatives

	Fertile (a)	Subfertile (b)	Not at risk (c)	Unknown (d)	Total (a+b+c+d)	Prevalence (b/a+b)·100%
Responder	116 (47.7%)	21 (8.6%)	106 (43.6%)	0 (0%)	243 (100%)	15.3
Brother	216 (56.7%)	8 (2.1%)	142 (37.3%)	15 (3.9%)	381 (100%)	3.6
Sister	237 (69.7%)	8 (2.4%)	58 (17.1%)	37 (10.9%)	340 (100%)	3.3
Maternal uncle	522 (82.5%)	16 (2.5%)	86 (13.6%)	9 (1.4%)	633 (100%)	3.0
Maternal aunt	550 (85.7%)	16 (2.5%)	51 (7.9%)	25 (3.9%)	642 (100%)	2.8
Paternal uncle	568 (85.0%)	8 (1.2%)	70 (10.5%)	22 (3.3%)	668 (100%)	1.4
Paternal aunt	555 (85.8%)	22 (3.4%)	52 (8.0%)	18 (2.8%)	647 (100%)	3.8
Nonresponder interview with phone	35 (34.7%)	3 (3.0%)	58 (57.4%)	5 (5.0%)	101 (100%)	7.9
Nonresponder interview without phone	. . .	. . .	. . .	109 (100%)	109 (100%)	. . .

or if childlessness was voluntary, or if a relative had died before 25 years of age, or if a relative was mentally retarded; and d) unknown, if the other categories did not apply.

We considered fertile and subfertile people to be ''at risk'' for fertility problems. The prevalence of subfertility was calculated for the group as a whole (b/a + b + c + d) and for the categories at risk for fertility problems (b/a + b).

Nonresponder Study

We tried to contact via telephone all men who had not responded to a reminder that was sent by post 2 weeks after the original questionnaire had been mailed. We gathered nonresponder data on 1) the reason for not responding, 2) the respondent's fertility status, and 3) subfertility among any of their relatives.

Side Study

A side study was performed in order to investigate the quality of the data that had been obtained through the questionnaire as opposed to data that would have been obtained through a personal interview, which is widely used in clinical settings. We contacted a sample of 80 responders whose responses had been stratified for the occurrence of subfertility, and asked them to participate in a personal interview.

Statistical Methods

We calculated the prevalence of subfertility by dividing the number of people with a fertility problem by the total number of people and by the number of people at risk for a fertility problem. We compared the calculated prevalences among the responders themselves and among their relatives by the use of odds ratios (ORs) and their 95% confidence intervals (CIs).

Because we sent questionnaires to a randomly selected group of men, we assume that the prevalence of subfertility among these men should be equal to that of their brothers. Therefore, an OR smaller than 1 suggests that subfertility among relatives is underreported.

In the side study we calculated kappa values, which indicate the chance-adjusted reproducibility of the data using a personal interview instead of a questionnaire. A kappa value of 1 indicates a perfect reproducibility. A kappa value of zero indicates that agreement is no better than chance.

Results

Questionnaire

After mailing the reminder, 264 out of 474 (55.7%) men responded. Two-hundred nine responders completed all questions, 34 men did not provide details on their second-degree relatives, and 21 men completed only the medical history form and did not provide details on their family history. In our analysis we included all 243 men (51.3%) who completed the questionnaire on at least their first-degree relatives.

The mean age of responders was 33.3 (SD 4.4) years. An abnormal andrologic history was present in 39 (16%) of the responders: a history of inguinal hernia in 19 (8%) men, male genital infection in 10 (4%), maldescended testis in 6 (3%), surgical correction of a varicocele in 3 (1%), and 1 man reported a testicular torsion.

The table displays the fertility status of responders and their relatives. Subfertility among responders was reported in 8.6% (21/243) of the total group, and 15.3% (21/137) in the at-risk group. The prevalence of reported subfertility among all subgroups of relatives was significantly lower than among responders. The responders reported a 5 times lower prevalence of subfertility among their brothers than among themselves (OR 0.2, 95% CI 0.08–0.5).

According to responders, their own subfertility was caused by unknown factors in 10 (48%), by female factors in 4 (19%), by male factors in 3 (14%), and by combined male and female factors in 4 (19%) out of 21 cases. Responders did not report subfertility among their parents and grandparents.

The number of men not at risk was not significantly different between responders and their brothers (42.4% and 37.3%, respectively). The reasons for the unproven fertility among brothers were voluntary childlessness (52.8%) and the absence of a heterosexual partner (47.2%).

Nonresponder Study

We were able to gather nonresponder information through contacts by telephone from 101 men in the group of 210 nonresponders (48.1%). The mean age of nonresponders was 32.8 years (SD 4.8), which was not significantly different from the mean age of responders. The major reasons for not responding were lack of time and a misunderstanding that the study was designed to focus only on people with proven fertility. The results from the nonresponder investigation are also shown in the table. The prevalence of subfertility (OR 0.47, 95% CI 0.1–1.7) did not differ significantly between nonresponders and responders.

Side Study

We contacted by telephone a sample of 80 responders whose responses were stratified for fertility problems in order to ask them to participate in the side study. We were able to interview 40 responders. Twenty-seven (34%) responders declined to participate and it was practically impossible to set up a meeting with the other 13 (16%) responders. Compared with the questionnaire, in personal interviews subfertility was reported more often among responders as well as among their relatives. Prevalences rose from 12% to 16% in responders, from 2.2% to 3.7% in first-degree relatives, and from 1.6% to 2.4% in second-degree relatives. However, kappa values for reported subfertility among responders, first-degree relatives, and second-degree relatives were high at 0.96, 0.87, and 0.77, respectively, although these high values are partly caused by the low prevalence of fertility problems.

Discussion

In this study we show that the prevalence of subfertility among relatives is most probably underestimated when data are collected using a family history. The prevalence of subfertility among responders in this survey (15.3%) is in the same range as in earlier reports (Hull et al, 1985; Beurskens et al, 1995). However, reported prevalence of subfertility among relatives was much lower than among responders. Brothers who did not differ significantly in age from responders were reported to have a 5 times lower prevalence of subfertility. The prevalence of subfertility was also significantly lower among responders' second-degree relatives.

Several factors may contribute to a lower reported prevalence of subfertility among relatives. The nonresponder study and the personal interview showed that the differences in prevalence of fertility problems were not caused by a low response to this survey or by the use of a questionnaire.

Misclassification is the most logical explanation for the differences found between responders and relatives. Relatives who were reported to be fertile may have been wrongly classified in this study because the responder may not have been aware of the presence of a fertility problem. This information bias or *taboo* bias could be caused by the difficulty of discussing subfertility in particular, or health problems in general, within the family. Research on donor insemination has shown that the stigma associated with infertility prompts secrecy and lack of openness (Turner and Coyle, 2000). Adding a control question in the questionnaire (eg, on diabetes) would have provided more information on the possible causes of underreporting fertility problems (eg, ignorance or recollection bias about health problems among relatives in general).

Similar forms of bias may also have occurred in the studies by Lilford et al (1994) and Meschede et al (2000), who reported no subfertility among relatives in their fertile control groups.

A possible explanation for the fact that in 10.9% of the sisters the fertility status is unknown may be that fertility problems are more easily discussed with a relative of the same gender. However, this difference is not present among second-degree relatives, and it demonstrates the low validity of the data obtained by taking a family history.

The side study showed that using a questionnaire to detect subfertility among relatives is not a considerably better tool than a personal interview. Using a questionnaire to obtain information on family history can be a cost-effective substitute for a personal interview when time or personnel are scarce. However, both methods will never reach results that are as accurate as the use of medical records to verify fertility status among relatives.

The taboo on discussing subfertility with relatives may be the reason why permission to contact subfertile relatives in these family studies on male subfertility is often withheld (personal observation).

What is the value of taking a family history in clinical and scientific practice? Our findings suggest that in the occurrence of a negative family history, one should still consider the possibility of familial subfertility unless all family members are proven fertile. A positive family history does provide useful information; however, because of taboo bias underreporting is likely, and checking via medical records can give better insight into patterns of inheritance and risk identification.

In conclusion, news about subfertility spreads selectively throughout families, causing information bias. We suggest further research on the use of family history for the purpose of investigating the additional value of direct contact with family members and validation of information through medical records. At this moment, researchers and clinicians should be aware that taking a family his-

tory on subfertility, as recommended by the American Society for Reproductive Medicine, is likely to underestimate subfertility among relatives.

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