5 Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet* 1991;**48**:232-42.
6 St John DJB, McDermott FT, Hopper JL, Debney EA, Johnson WR, Hughes ES. Cancer risk in relatives of patients with common colorectal cancer. *Ann Intern Med* 1993;**118**:785-90.
7 Ford D, Bliss JM, Swerdlow AJ, Armstrong BK, Franceschi S, Green A, Holly EA, Mack T, MacKie RM, Osterlind A, Walter SD, Peto J, Easton DF. Risk of cutaneous melanoma associated with a family history of the disease. *Int J Cancer* 1995;**62**:377-81.
8 Burke W, Culver JO, Bowen D, Lowry D Durfy S, McTiernan A, Anderson MR. Genetic counselling for women with an intermediate family history of breast cancer. *Am J Med Genet* 2000;**90**:361-8.
9 Evans DG, Burnell LD, Hopwood P, Howell A. Perception of risk in women with a family history of breast cancer. *Br J Cancer* 1993;**67**:612-14.
10 Meiser B, Butow P, Barrat A, Gattas M Gaff C, Haan E, Gleeson M, Dudding T, Tucker K, and the Psychological Impact Collaborative Group. Risk perceptions and knowledge of breast cancer genetics in women at increased risk of developing hereditary breast cancer. *Psychol Health* (in press).
11 Dimond E, Calzone K, Davis J, Jenkins J. The role of the nurse in cancer genetics. *Cancer Nurs* 1998;**21**:57-70.
12 Calzone K, MacDonald D, Tranin AS. Readers comment on the nursing role of cancer genetics. *Oncol Nurs Forum* 1995;**22**:887-8.
13 Loescher L. Genetics in cancer prediction, screening and counselling. Part II. The nurse's role in genetic counselling. *Oncol Nurses Forum* 1995;**22**:16-19.
14 MacDonald DJ. The oncology nurse's role in cancer risk assessment and counseling. *Semin Oncol Nurs* 1997;**13**: 123-8.
15 Guskey T. *Implementing mastery learning*. Belmont, USA: Wadsworth, 1985.
16 Board of Censors in Genetic Counselling. *Training guidelines*. Human Genetics Society of Australasia, 1999.
17 Stoll BA. Specialist breast and ovarian cancer clinics should be staffed by oncology nurses. *BMJ* 1996;**312**:913.

Participation in preconceptional carrier couple screening: characteristics, attitudes, and knowledge of both partners

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J Med Genet 2001;**38**:695–703

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EDITOR—Couples in which both partners are carriers for a particular autosomal recessive disease, such as cystic fibrosis, Tay-Sachs disease, or thalassaemia, have a 1 in 4 risk for each child to have this disorder. Population carrier screening programmes aimed at the identification of carrier couples make it possible to inform these couples about their risk and about the reproductive options that are available. Before beginning any genetic screening programme, it is important to assess community interest in screening.[1]

It is well known that the way in which carrier screening is offered and the timing, for example, during or outside pregnancy, determine participation in screening and the reasons for participation. Screening offered face to face with the possibility of immediate testing gives high uptake rates, whereas offers made by mailed invitation or poster announcements attract little interest.[2–6]

Most of the data on motives for participation have been obtained from programmes offering carrier screening during pregnancy.[7–15] In these studies, a high interest in screening was reported, although it has been argued that testing during pregnancy is often accepted just because it is offered.[16] The decision to participate was mostly made by women, who were often initially tested without discussing it with their partner. Anxiety has been reported among those who are tested positive, while waiting for their partner's results.[10 17 18] It can also cause distress when the partner is not available or does not want to be tested.[19] Furthermore, prenatal screening leaves limited reproductive options for a carrier couple and might impose time constraints when decisions about a prenatal diagnosis have to be made.[20] Offering carrier screening outside pregnancy shows low participation rates when no pregnancy is planned, but interest is higher when there are plans for having children (preconceptional).[4 7 21]

This study focused on the preconception period as the time for screening and considered couples as the screening unit. Determining why some couples participate in a preconceptional carrier screening programme while others decline provides insight into the desirability of screening. It may also give some indications of how to improve accessibility to screening for those who are interested. To investigate this, couples can be directly asked for reasons why they decided (not) to participate. In addition, determining differences in individual variables and attitudes between participants and non-participants can be used to explain participation. Early theories on health related behaviour suggest that intention to take a preventive health action is likely when people (1) view themselves as susceptible to the condition, (2) consider the disease to be serious, (3) perceive high benefits of the health action, and (4) perceive few disadvantages in undertaking it.[22] These four components are the earliest constructs of the Health Belief Model (HBM), which has been considerably expanded, as was reviewed by Janz and Becker.[23] The present study focused on a select group of variables derived from the HBM. This model was chosen because of its applicability to predicting behaviour towards voluntary action, such as carrier screening.

In this study, the determinants of participation in preconceptional cystic fibrosis (CF) carrier couple screening was investigated, focusing on the characteristics and attitudes of

both partners. The study was carried out within the framework of a large project on the feasibility and desirability of CF carrier screening in The Netherlands. It was designed to address the following research questions. What is the main reason why couples choose to participate or choose not to participate in carrier couple screening? Are there HBM related factors associated with participation among eligible couples invited for screening?

Subjects and methods

PROCEDURES

Participating and non-participating couples were recruited from a feasibility study of preconceptional CF carrier couples screening in The Netherlands. Screening was offered to couples who were considering a pregnancy in the future, by five general practices, between May 1997 and June 1998. In total, 5414 people, aged 20 to 35 years, received a letter of invitation signed by their general practitioner (GP). GPs were asked to exclude patients with fertility problems or psychosocial problems from the mailing list to avoid any possible emotional disturbance of these people by the invitation. The letter invited couples, interested in screening, to attend a 45 minute educational session at a nearby location on two evenings in one week. The letters were non-directive, did not encourage couples to participate, and mentioned that this was a scientific study on interest in participation. Both partners were asked to be present. Enclosed with the letter was an information leaflet. The leaflet described the clinical and genetic aspects of CF, carrier prevalence in the population, the implications for the couple of a positive carrier screening test, and how testing is conducted, including information about the imperfect sensitivity of the test (the test sensitivity in this study was approximately 87%). A member of the research group (LH) organised the educational sessions. At the session, attendees were given more detailed information, and an outline of possible advantages and disadvantages of screening was presented. At the end of the session, couples were offered the carrier test, which would be performed by mutation analysis on a mouthwash sample. All of this was offered free of charge. Exclusion criteria for the participation of couples were: pregnancy, a positive family history of CF, and age younger than 18 years. Both partners of participating couples provided a mouthwash sample. If only one partner was able to attend the session, a kit was provided in which the mouthwash sample of the other partner could be collected at home. After the educational session, couples were given an informed consent form to take home and were asked to return it by mail within one week. The Medical Ethical Committee of the academic hospital Vrije Universiteit in Amsterdam approved the study protocol.

UPTAKE

To determine the uptake of screening, a non-response survey by telephone was performed to estimate the percentage of eligible persons in the invited population. Eligibility was defined as having a steady relationship and planning to have one or more children with the partner. A random, age stratified sample of those who did not respond to the initial invitation for screening, that is, did not attend the educational session, was contacted by telephone on different evenings during the week. Other random subjects replaced those who did not answer the telephone after three calls until samples of approximately 10% (n=387) in every practice were reached. Respondents were asked whether they had received the letter of invitation from their GP, whether they were interested in screening, and whether their situation conformed to that of the target population. The non-response telephone survey showed that 19.6% (76/387) of these invited subjects were eligible for participation. In the calculation of uptake rates, the responses of subjects to the invitation were considered, and not the responses of couples, since invitations were sent to individual people and some partners did not receive an invitation because their age group was not included or because they had a different GP. Subjects whose mail was returned by the post office as undeliverable (n=99) were excluded from the study. In total, 108 subjects (related to 79 couples) responded to the invitation for screening. The response therefore was 2% of the total population (108/5315) and 10.4% of the eligible (target) population (108/1042). Seventy eight couples consented to participate in the test (78/79, 98.7% participation) after the educational session.

COMPARISON OF PARTICIPANTS AND NON-PARTICIPANTS

To determine factors influencing the decision to accept the test, differences between consenting couples (participants) and a sample (see below) of eligible couples who did not attend the screening session, identified through the non-response telephone survey (non-participants), were investigated. Data were gathered by means of questionnaires that were identical for both partners and both groups. Questionnaires were administered to all attendants at the beginning of the educational session. Each partner in a couple was asked to complete the questionnaire individually without consulting the other partner. Of the 78 participating couples, 76 completed the questionnaire.

Non-participants who confirmed during the non-response telephone survey a desire to have children with their partner, that is, they were eligible for participation (n=76), were asked whether they and their partner would be willing to complete the questionnaire and return it by mail. Of these 76 non-participants, six did not wish to take part in the study. In total, 76% (53/70) of the non-attending eligible couples returned the questionnaire. Those who did not return the questionnaire (n=17) had previously reported by telephone that their main reason for non-participation was lack of time. Eventually, 76 participating and 53 eligible non-participating couples could be compared.

QUESTIONNAIRE DESIGN

The questionnaire was developed and tested for homogeneity specifically for this study. Subjects were asked, in an open ended question, to indicate the single most important reason for participating or not participating in the screening. In addition, they were asked to report which partner (both partners, man, or woman) had influenced the decision most, and their agreement over the final decision (both agree, partner disagrees, or I disagree). Furthermore, the questionnaire assessed certain components of the Health Belief Model (HBM) including the following:

(1) Sociodemographics

Subjects provided information on age, gender, marital status, highest level of education, number of children, and religiousness. Couples were also asked to indicate whether a pregnancy was planned in the short term (within the next two years) or in the long term (after the next two years).

(2) Familiarity with the disease

Familiarity with the disease was derived from the response to the question: had you heard about the disease cystic fibrosis before receiving the invitation for screening?

(3) Knowledge of the disease

This consisted of seven multiple choice questions, assessing the level of understanding of the medical and genetic aspect of CF and carrier testing. A response of "don't know" was scored as an incorrect answer. The number of questions answered correctly was calculated as a sum score. The answers to the separate questions were also considered.

(4) Health locus of control

The validated subscale of the Multidimensional Health Locus of Control scale with the locus dimension "internal control" was used to indicate the extent to which subjects perceived their behaviour as responsible for their own health (IHLC).[24] According to this model, a person is more likely to engage in healthy behaviour if he or she has a strong internal locus of control. The subscale consists of six items, and the answering format was a six point Likert-type scale (completely agree (1) to completely disagree (6)). A total sum score was computed for each subject, with high scores indicating a higher likelihood of engaging in healthy behaviour. Cronbach's α for IHLC on the data was 0.76.

(5) Perceived discomfort

The respondents were asked to indicate the extent to which they agreed that screening requires too much of their time and effort (completely disagree (1) to completely agree (5)).

(6) Constructs of HBM

The questionnaire included 14 items specifically addressing carrier screening, to measure perceptions concerning carrier testing (see Appendix). The newly developed constructs were derived from the four basic HBM dimensions[22]: (1) perceived risk of being a carrier (couple) and having a child with CF ("Perceived susceptibility", three items), (2) perceived severity of the disease and the burden of treatment of a child with CF ("Perceived seriousness", three items), (3) benefits of testing ("Perceived benefits", five items), and (4) perceived barriers related to screening, such as worries about testing, the perceived impact of carrier status, and the perception that other people will look differently at them when they are identified as carrier ("Perceived impact barriers", three items). For "Perceived susceptibility", respondents were asked to indicate the estimated likelihood of their risk on a six point scale (very unlikely (1) to very likely (6)). For all other items, the respondents were asked to indicate the extent to which they agreed with each statement on a five point Likert scale (completely disagree (1) to completely agree (5)). Principal axis factor analysis with varimax rotation was performed to verify that the items loaded on the four factors of the HBM. Subsequently, a reliability analysis was performed on each scale to determine whether all items contributed to the internal consistency of the scale. Summing up items results in a single measure for three subscales with good reliability: "Perceived susceptibility" (Cronbach's α=0.83), "Perceived benefits" (Cronbach's α=0.90), and "Perceived impact barriers" (Cronbach's α=0.64). For "Perceived seriousness", the items (n=3) were considered separately, owing to the low internal consistency of the total scale.

DATA ANALYSES

To answer the first research question, the answers of couples to the open ended question about the main reason for participating or not participating in screening were coded into general categories. Before trying to answer the second research question, it was necessary to determine whether the data of both partners should be included as a pair, because both the man and the woman of each couple completed a questionnaire. To investigate this, the responses to questionnaires of both partners were compared, using McNemar non-parametric tests for categorical data and paired *t* tests for continuous data. Since the sociodemographic status was highly correlated between the partners within a couple, data of only one randomly selected partner were included in the bivariate analyses comparing participants and non-participants. For all the other variables (2) to (6), at first the median split of the sum scores was taken, which resulted in subjects with low scores and subjects with high scores (knowledge low (0-3), high (4-7); IHLC low (6-23), high (24-36); susceptibility low (3-9), high (10-18); benefits low (5-19), high (20-25); impact barriers low (3-6), high (7-14), and separate items (discomfort and seriousness) low (1-3), high (4-5)). Paired data analyses showed that in the responses to these variables, there were moderate to low associations between partners in a couple, indicating that both partners provide different information. Therefore, it was not possible randomly to select one partner of the couple for the analyses. In addition, since the attendance of a couple at the

educational session and participation in screening requires a joint decision, it was assumed that the association between a given variable and participation in screening would be stronger when partners have similar attitudes. To quantify the association between the scores of both partners of a couple, a concordance score was formed on a three point scale: 2="High-High" (both partners in a couple scoring high on the variable), 1="High-Low" (one partner scoring high (male or female) and one partner scoring low (male or female), and 0="Low-Low"' (both partners in a couple scoring low on the variable). Subsequently, bivariate analyses were performed to examine the association between participation in screening and the concordance variables (2) to (6). Chi-square analysis and Fisher's exact tests were used to compare responses between participating and non-participating couples. Finally, all variables (1) to (6) that showed statistical significance in bivariate analyses were entered into one multiple logistic regression model simultaneously. All analyses were performed using SPSS for Windows.[25] A p value of <0.05 was considered to indicate statistical significance.

Results

MAIN REASON GIVEN FOR PARTICIPATION AND NON-PARTICIPATION

Among the 76 couples who decided to attend the educational session and consented to CF carrier testing, the decision was taken jointly in 85%, while 15% reported that the woman had more influence on the decision to participate. Nevertheless, none of the couples reported disagreement on the final decision. The main reason given by couples for taking the test was that they wanted to know whether they were a carrier couple with a high risk of having a child with CF (97%). The other couples (3%) gave no specific reasons for taking the test. The reasons non-participants gave (in their own words) for not responding to the invitation for screening varied, but the most commonly stated reason for not attending the educational session" (53%, n=28). Other reasons given were that "the test results would not influence our attitudes towards family planning" (21%, n=11). Furthermore, 15% of the couples were not interested in testing because they "were not concerned" (n=6) or they had "never heard of CF" (n=2). Five percent reported "testing would make us too anxious". The answers of most partners in a couple could be placed in the same category. However, in three couples (6%), the partners showed disagreement; the women reported that they were interested in screening but they declined the test because their partners were reluctant to participate.

*Table 1 Sociodemographic characteristics of participants and non-participants in a preconceptional CF carrier screening programme**

	Participants (76 couples)		*Non-participants (53 couples)*	
	Women (n=76)	*Men (n=74)*	*Women (n=53)*	*Men (n=52)*
Age (mean (range))	28.5 (20–44)	30.9 (20–45)§	27.6 (20–37)	30.4 (23–41)§
Marital status (% married)	45	45	45	46
Level of education† (%)				
Low	13	16	19	23
Medium	42	42	51	40
High	45	42	30	37
Children (% having children)	26	27	42	42
Planning children (% within 2 years)	55	49	62	58
Religion‡ (%)				
No religion	47	52	53	59
Religion, irregular practice	49	43	34	31
Religion, regular practice	4	5	13	10

For three couples, sociodemographic data for the man were missing.
*Age was evaluated by *t* test; all other characteristics were evaluated by chi-square.
†Low: primary school, lower level of secondary school, lower vocational training. Medium: higher level of secondary school, intermediate vocational training. High: higher vocational training, university.
‡Irregular practice: church attendance <1 month. Regular practice: church attendance ⩾1 month.
§Significant at $p<0.05$ for comparison of men and women within the couples.

FACTORS ASSOCIATED WITH PARTICIPATION

Sociodemographics of participants and non-participants, both men and women, are shown in table 1. Within the couples included in the study, no statistically significant differences were found between men and women with regard to educational level, time period in which children were planned, and religiousness. The men were significantly older than the women in both participating and non-participating couples. In general, within a relationship, men are older than women in The Netherlands.[26] In bivariate analyses, no associations could be shown between participation and the variables age, marital status, level of education, number of children, the time period for planning children, or religiousness.

While the sociodemographics for both men and women within the couples were highly comparable, paired data analyses showed that in the responses to the other variables, such as familiarity with CF, knowledge of CF, and perceptions with regard to carrier screening, there were differences between partners. Therefore, data of both partners were included in the subsequent analyses. Table 2 shows the bivariate associations between components of the Health Belief Model and participation in screening for the three different concordance groups ("High-High", "High-Low", "Low-Low"). Participating couples scored higher than non-participating couples on the knowledge questionnaire, and higher on the internal health locus of control (IHLC) scale and perceived higher benefits of testing. In addition, participating couples were more likely than non-participating couples to perceive low discomfort of screening and low impact barriers to screening. No associations were found between participation in screening and familiarity with CF, perceived susceptibility, or the items on perceived seriousness. Furthermore, no differences in responses were found between the five general practices that participated in offering the screening.

The relevant components found in the bivariate analyses were entered into one multiple logistic model simultaneously. Coefficients, odds ratios (OR), 95% confidence intervals (95% CI), and p values for this model are presented in table 3. Perceived discomfort and perceived benefits appeared to be the strongest predictors for participation in screening. Couples in which both partners perceived low discomfort of screening were more likely to

Table 2 Bivariate associations of components of the Health Belief Model and concordance variables of participating and non-participating couples*

	Participants n=76 couples (%)	*Non-participants n=53 couples (%)*
Familiarity with the disease		
Yes-Yes	34	28
Yes-No	36	30
No-No	30	42
Knowledge of the disease		
High-High	62	34***
High-Low	26	25***
Low-Low	12	41***
IHLC†		
High-High	33	23**
High-Low	40	24**
Low-Low	27	53**
Perceived discomfort		
High-High	0	11***
High-Low	3	23***
Low-Low	97	66***
Perceived susceptibility		
High-High	1	4
High-Low	13	8
Low-Low	86	88
Perceived benefits		
High-High	77	34***
High-Low	18	26***
Low-Low	5	40***
Perceived impact barriers		
High-High	5	38***
High-Low	32	38***
Low-Low	63	24***
Burden of disease		
High-High	67	55
High-Low	17	24
Low-Low	16	21
Burden of child with disease		
High-High	75	64
High-Low	18	25
Low-Low	7	11
Burden of treatment		
High-High	22	19
High-Low	38	26
Low-Low	40	55

For five couples, data for only one partner were available. In the analyses, data of the available partner were used for the missing data of the other partner. Analyses without these five couples showed the same results.
*High-High/Yes-Yes (both partners of a couple scoring High/Yes on the variable). High-Low/Yes-No (one partner scoring High/Yes (male or female) and one partner scoring Low/No (male or female)). Low-Low/No-No (both partners of a couple scoring Low/No on the variable).
†Internal health locus of control scale.
Chi-square tests for comparison of participating and non-participating couples, **p<0.01, ***p<0.001.

participate than couples in which at least one partner perceived high discomfort of screening. Compared to couples perceiving low benefits from screening, couples in which one or both partners perceived high benefits were more likely to participate. Couples in which both partners perceived low impact barriers were more likely to have the test than couples in which both partners perceived high barriers. Couples with high knowledge scores were more likely than couples with low knowledge scores to participate in screening. Finally, couples with one partner scoring high on the internal health locus of control scale were more likely to participate than couples with low scores.

ATTITUDES OF COUPLES WITH DIFFERENT REASONS FOR NON-PARTICIPATION

Over half of the couples who did not attend the educational session (53%) reported that the main reason for non-participation was that they had no time or had forgotten to attend the educational sessions. These couples may differ in their attitude towards testing from the other non-participating couples. To analyse this, couples who did not attend were divided into two subgroups: (1) those who reported that they had no time or had forgotten to attend, but were possibly interested in screening ("lack of time", n=28), and (2) those who did not attend for other reasons ("other reasons", n=25). Bivariate analyses of the variables (1) to (6) showed that only one variable was associated with reporting "lack of time". In non-participating couples reporting "lack of time", it was more likely that both partners perceived high benefits of screening than in non-participating couples reporting "other reasons" (50% *v* 16%) (OR=8.7 (2.0-37.7)). In addition, two-thirds of these couples perceiving high benefits and reporting "lack of time" had high knowledge scores.

Of all non-participants, 76% supported the view that genetic carrier testing for CF should be offered to all couples planning to have children, 15% did not favour this opinion, and 9% were not sure. Among those who reported "lack of time", only two respondents were opposed to offering screening in the general population.

PARTICIPANT AND NON-PARTICIPANT KNOWLEDGE

With regard to more detailed knowledge of CF, a comparison was made of correct answers of participants (before the educational session) and non-participants to five multiple choice questions on the knowledge questionnaire. The answers to these questions could all have been found in the information leaflet, which was sent with the letter of invitation for screening. Participants were significantly more likely than non-participants to be aware of the most important symptoms of CF (64% *v* 32%), to know that carriers do not need to have a family history of CF (83% *v* 69%), to recall the risk of being a CF carrier (61% *v* 39%), and to

Table 3 Multiple logistic regression model: odds of participation of couples in CF carrier screening

Predictor	*Odds ratio (95% CI)*
Knowledge of disease	
High-High	6.1 (1.5–24.9)**
High-Low	3.2 (0.8–13.5)
Low-Low	Ref
*IHLC**	
High-High	2.3 (0.7–8.1)
High-Low	5.2 (1.4–19.4)**
Low-Low	Ref
Perceived discomfort†	
High-High/High-Low	Ref
Low-Low	19.2 (2.9–125.5)***
Perceived benefits	
High-High	16.2 (3.8–69.1)***
High-Low	7.9 (1.6–39.4)**
Low-Low	Ref
Perceived impact barriers	
High-High	Ref
High-Low	3.7 (0.8–17.5)
Low-Low	7.0 (1.5–32.2)**

Ref = reference category.
*Internal health locus of control scale.
†In the analyses, the subgroups High-High and High-Low were added together, to account for empty cells in the subgroup High-High.
**p<0.05, ***p<0.01.

understand that carriers of CF would not develop CF related health problems (66% *v* 41%). There was no association between knowledge scores and level of education. In both groups, women scored higher on the knowledge questionnaire than men. In addition, more women than men had previously heard of CF.

Discussion

In this study, factors associated with participation in preconceptional carrier couple screening were assessed. The results suggest that couples who participated in the CF carrier screening programme, as opposed to those who did not, perceived lower discomfort from screening, perceived higher benefits, perceived lower impact of the consequences of screening, knew more about CF, and perceived their own behaviour to be responsible for their health. Overall, the results were more pronounced when partners had similar perceptions. The main reason given for not participating in screening was lack of time to attend the educational session. The results showed that couples who lacked the time to attend perceived more benefits from screening than couples reporting "other reasons" for non-participation.

As expected, higher perceived benefits of the test were associated with more participation in screening. Benefits from testing reflect the importance couples attach to knowing their chances of having a child with CF, which was also found to be the most frequently reported reason for participation in screening. It also reflects the expectations of the couples that they will have more reassurance and that the test results will help them to make decisions about having children. Higher awareness of the benefits of screening may increase the acceptance and participation of couples in screening. In 34% of the non-participating couples, the perception of the discomfort of screening was high for at least one partner. These couples will probably only participate if screening takes less of their time and does not require an extra visit. The results also suggest that those who perceive low impact barriers, such as the impact of carriership on their general health status and the perception that other people will look differently at them, are more likely to accept screening. Only 41% of all non-participants stated correctly that carriers of CF would not develop health problems resulting from their carrier status. These results suggest that anxiety about screening and the burden of carrier status are partly based on misconceptions owing to lack of knowledge.

Knowledge of CF was also a predictor for participation in screening, although this is probably more a reflection of the interest couples have in screening and reading the leaflet before attending the educational session than knowing about CF before the invitation for screening. Nevertheless, inadequate understanding could lead to increased anxiety, and therefore result in non-participation. Bernhardt *et al*[27] stated that better baseline understanding of human genetics in the public might provide a basis for understanding genetic screening tests and increase interest in learning about screening tests.

The percentage of respondents who were familiar with CF is comparable with the percentages in the Dutch population in general, in which 60% know about the disease and 15% know somebody with CF.[28] Familiarity with the disease was not associated with participation. This could be explained by the fact that people may have heard about CF, but do not know the clinical implications or the hereditary pattern of the disease. Possibly therefore, this variable was not a motivating factor in participation.

Studies have shown that people are more likely to participate in screening if they consider themselves susceptible to being a carrier or to having an affected child.[4 12 29 30] This is in contrast with the finding of the present study, in which no association was found between perceived risk and participation. Most respondents thought it very unlikely that they would be a carrier or that they would have a child with CF. The percentage of respondents knowing the carrier risk was 61% in the participants and 39% in the non-participants. Again, this might imply that non-participation is partly based on lack of knowledge and the assumption that CF is not very common. The question remains as to whether a more accurate understanding of actual risk might have led to a different perception of risk, which would influence participation. A previous study has shown that perceived risk, rather than actual risk, influences the participation of women in prenatal screening tests.[31] Presumably, couples participate because they want to be reassured that their risk is low, and not because there is a chance of their being carriers or having a child with CF. This is supported by the findings of Loader *et al*[12] that the desire for reassurance of a low risk of having a child with CF was mentioned twice as often (50.6%) as the intention to avoid having such a child (27.8%).

Other studies[4 29] have also reported the lack of an association between perceived seriousness of the disease itself and participation in screening. In the present study, the burden of the disease and the burden of a child with CF was perceived as high for most respondents, whereas the impact of treatment was perceived as moderate to low. This suggests that respondents perceive CF as a very serious disease, but think they can cope with a sick child in practice. In the present study, no influence of the level of education on participation was found, which is in contrast with the findings of other studies.[4 12 13 21 29] Furthermore, already having children was not found to be a reason to decline screening, suggesting that the couples understood this aspect of inheriting CF. Overall, 45% of the couples were married, as expected from this age group in the Dutch population.[25]

The effect of factors predicting participation in screening was more pronounced when couples shared their views. To our knowledge, only one other study[29] described the agreement of

husband and wife in predicting participation in a carrier screening programme. In this study, it was found that the combined beliefs of couples increased precision in the prediction of who will participate in screening for Tay-Sachs disease.

In the present study it was stressed that both partners should attend the educational session to receive the same information, on which subsequent decision making could be based. Of all participating couples, 15% reported that the decision to accept screening was merely the woman's decision, whereas 6% declined because the male partner did not wish to participate. The results also showed that women had heard about CF more often than men and knew more about the disease. Overall, these results are consistent with the findings of other studies,[3 5–7 21 32] that is, that interest in testing is greater among women than among men. This may reflect the greater concern and responsibility in reproductive decisions felt by women. Future analyses of additional data will be performed to determine whether gender differences in the response to the test results can be found, as has been reported in other studies.[33 34]

Lack of time was the most frequently reported reason for non-participation. The invitation to attend the educational session on two evenings in one week was sent 14 days in advance. This might have been too short for people who already had other appointments on these evenings. Moreover, it has been found that when screening is offered a second time, on more evenings, or when people can make their own appointment, for example with their own GP, participation increases (Henneman *et al*, in preparation). Although not reported, another reason for non-participation might be that couples prefer personal counselling instead of attending a general educational session with other couples. In a study carried out by Clayton *et al*,[6] non-pregnant couples showed lack of interest in carrier screening. Reluctance to participate was ascribed to worries about factors such as insurability, being at risk, what they would need to learn, abortion, and religious beliefs. However, the authors believe that lack of interest in that study might also be explained by the mode of invitation, letters placed in pockets on signs and not personally addressed to those who were offered screening. Mode of invitation has been found to be the most important factor influencing acceptance.[2–4] Invitations that were more personal might have increased interest in that specific screening programme. In prenatal carrier screening, unwillingness to terminate an affected pregnancy was mainly found to be the most frequently reported reason to decline screening,[9 12 35] although lack of time has also been reported.[14]

The uptake of the pre-educational screening session of couples who planned to have children was 10.4% in the present study. This uptake is not high, compared with other screening programmes offered before pregnancy[2 3 5] and during pregnancy.[9 10 13 36] However, the authors are of the opinion that uptake rate is not the most important determinant, if not for economic reasons, of the desirability of screening. Yet, knowledge about motives and barriers for participation is important. As Marteau[37] also emphasised, one of the key research questions for the next 10 years should be to find the best way of offering tests to achieve informed choice. In the present study, the main reason couples gave for participation in the screening was to find out whether they were at high risk of having a child with CF. None of the couples reported that they participated in the screening because they were told to do so by their GP or that they felt that they could not refuse. These results suggest that because of the time and effort needed for participation, couples were stimulated to make a decision based on the conviction that screening is important, and not just because it is offered or strongly recommended, as was argued for opportunistic screening programmes with high uptake rates.[36 38]

For this study, new scales based on the Health Belief Model (HBM) were developed to evaluate the response of couples to CF carrier screening. Several other components of the HBM, that were not addressed in the present study for practical reasons, may also be important, such as interpersonal interactions and mass media communications,[22] and the influence of psychological defence mechanisms, such as avoidance behaviour.[30] There has also been more general criticism of the model, like other rational choice theories, that is, that it provides an idealised view of how decisions should be made and that it gives insufficient attention to emotion in decision making and the role of cultural standards and values.[39] However, the HBM provided more insight into the motives and barriers reported by couples who were offered carrier screening. In addition to HBM related variables, other variables are also considered to be important in affecting participation in carrier screening, such as tolerance of test uncertainty.[4]

This article specifically addressed the participation in preconceptional CF carrier screening in The Netherlands. Differences between other screening programmes and other countries will exist, but many similarities are evident, and the results of this study can be used in the development of other programmes. Preconceptional screening was chosen because it provides a maximum number of reproductive options for identified carrier couples and involves a minimum of (time) constraint. Furthermore, there are three other reasons why preconceptional screening is highly applicable in The Netherlands. Firstly, prenatal screening is difficult for practical reasons, because many pregnant women visit a clinic late in their pregnancy. Secondly, preconceptional screening meets the requirements formulated by the Committee for Genetic Screening of the Dutch Health Council, whereas prenatal screening does not.[40] Thirdly, there are a large number of planned pregnancies in The Netherlands (85-90%), creating an ideal situation for contacting couples before conception. These reasons may also be valid for other countries. In

Appendix

Constructs of the Health Belief Model: subscales and items with good reliability and associated α (n=3) and separate items of subscales with low reliability (n=1)

Subscales:	*Perceived susceptibility (Cronbach's α 0.90)*	
	• Estimated likelihood of being a CF carrier	
	• Estimated likelihood of being a CF carrier couple	
	• Estimated likelihood of having a child with CF	
	Perceived benefits (Cronbach's α 0.83)	
	• Carrier testing gives me more reassurance	
	• It is important for me to know if I am a carrier	
	• It is important for me to know my risk of having a child with CF	
	• The test results will help me to make childbearing decisions	
	• Carrier testing should be offered to all couples who are planning to have children	
	Perceived impact barriers (Cronbach's α 0.64)	
	• If I had carrier testing, I would feel worried	
	• If I were a carrier, I would feel less healthy	
	• If I were a carrier, people would look differently at me	
Separate items:	*Perceived seriousness of disease**	
	• CF is one of the worst diseases there is (burden of disease)	
	• I would find it hard if my child had CF (burden of child with disease)	
	• I would find it hard to give my child the treatment (burden of treatment)	

*Cronbach's α less than 0.40.

addition, preconceptional screening can be considered for a number of other reasons, as has recently been suggested for Tay-Sachs disease[41] and haemoglobin disorders.[42 43] For example, in the UK, prenatal screening for haemoglobin disorders is recommended as a routine practice,[44] although it has been shown that the present practice does not always meet the needs for early information and leads to the late recognition of risk.[45 46] Moreover, at the beginning of a thalassaemia screening programme[43] in Sardinia in the mid 1970s, the largest category of participants consisted of pregnant women, whereas the number of couples without a pregnancy is currently increasing. In other countries, however, cultural differences influence the approach to carrier screening.[47] For example, screening is offered premaritally to communities of Orthodox Jews, to prevent the marriage of two carriers of recessive disorders.[48]

In this study, interest in preconceptional CF carrier screening, requiring time and effort to participate, is shown, both by the actual participation of couples and by the perceived benefits of screening of couples who did not participate. The results of the study could be used as a model for other screening programmes. Lack of time to attend the educational session was found to be the main influence on participation in carrier screening by non-pregnant couples. However, the results suggest that these couples have positive attitudes towards screening and will attend when screening is offered more conveniently. The results also indicate that participation is influenced by "psychological" barriers, possibly caused by an inadequate understanding of the consequences of carrier testing. These barriers could be removed by providing more clear information about the meaning of carrier status and by increasing public awareness. In addition to participation in screening, the psychological and cognitive consequences of screening are being investigated.

The authors thank the participating general practitioners for their cooperation in this project, and especially Henk de Vries. This project was supported by the Vrije Universiteit Medical Centre Amsterdam and by grant No 2827030 from The Netherlands Health Research and Development Council.

1 Wilfond BS, Thomson EJ. Models of public health genetic policy development. In: Khoury MJ, Burke W, Thomson EJ, eds. *Genetics and public health in the 21st century. Using genetic information to improve health and prevent disease*. Oxford: Oxford University Press, 2000:61-81.
2 Watson EK, Mayall E, Chapple J, Dalziel M, Harrington K, Williams C, Williamson R. Screening for carriers of cystic fibrosis through primary health care services. *BMJ* 1991;**303**:504-7.
3 Bekker H, Modell M, Denniss G, Silver A, Mathew C, Bobrow M, Marteau T. Uptake of cystic fibrosis testing in primary care: supply push or demand pull? *BMJ* 1993;**306**: 1584-6.
4 Tambor ES, Bernhardt BA, Chase GA, Faden RR, Geller G, Hofman KJ, Holtzman NA. Offering cystic fibrosis carrier screening to an HMO population: factors associated with utilization. *Am J Hum Genet* 1994;**55**:626-37.
5 Payne Y, Williams M, Cheadle J, Stott NC, Rowlands M, Shickle D, West G, Meredith L, Goodchild M, Harper PS, Clarke A. Carrier screening for cystic fibrosis in primary care: evaluation of a project in South Wales. The South Wales Cystic Fibrosis Carrier Screening Research Team. *Clin Genet* 1997;**51**:153-63.
6 Clayton EW, Hannig VL, Pfotenhauer JP, Parker RA, Campbell PW, Phillips JA. Lack of interest by nonpregnant couples in population-based cystic fibrosis carrier screening. *Am J Hum Genet* 1996;**58**:617-27.
7 Kaback MM, Becker MH, Ruth MV. Sociologic studies in human genetics. I. Compliance factors in a voluntary heterozygote screening program. *Birth Defects* 1974;**10**: 145-63.
8 Rowley PT, Loader S, Sutera CJ, Walden M, Kozyra A. Prenatal screening for hemoglobinopathies. III. Applicability of the health belief model. *Am J Hum Genet* 1991;**48**:452-9.
9 Mennie ME, Gilfillan A, Compton ME, Liston WA, Brock DJ. Prenatal cystic fibrosis carrier screening: factors in a woman's decision to decline testing. *Prenat Diagn* 1993;**13**: 807-14.
10 Miedzybrodzka ZH, Hall MH, Mollison J, Templeton A, Russell IT, Dean JCS, Kelly KF, Marteau TM, Haites NE. Antenatal screening for carriers of cystic fibrosis: randomised trial of stepwise v couple screening. *BMJ* 1995;**310**:353-7.
11 Harris HJ, Scotcher D, Hartley NE, Wallace A, Craufurd D, Harris R. Pilot study of the acceptability of cystic fibrosis carrier testing during routine antenatal consultations in general practice. *Br J Gen Pract* 1996;**46**:225-7.
12 Loader S, Caldwell P, Kozyra A, Levenkron JC, Boehm CD, Kazazian HH, Rowley PT. Cystic fibrosis carrier population screening in the primary care setting. *Am J Hum Genet* 1996;**59**:234-47.
13 Witt DR, Schaefer C, Hallam P, Wi S, Blumberg B, Fishbach A, Holtzman J, Kornfeld S, Lee R, Nemzer L, Palmer R. Cystic fibrosis heterozygote screening in 5,161 pregnant women. *Am J Hum Genet* 1996;**58**:823-35.
14 Grody WW, Dunkel-Schetter C, Tatsugawa ZH, Fox MA, Fang CY, Cantor RM, Novak JM, Bass HN, Crandall BF. PCR-based screening for cystic fibrosis carrier mutations in an ethnically diverse pregnant population. *Am J Hum Genet* 1997;**60**:935-47.
15 Modell B, Harris R, Lane B, Khan M, Darlison M, Petrou M, Old J, Layton M, Varnavides L. Informed choice in genetic screening for thalassaemia during pregnancy: audit from a national confidential inquiry. *BMJ* 2000;**320**:337-41.
16 Hartley NE, Scotcher D, Harris H, Williamson P, Wallace A, Craufurd D, Harris R. The uptake and acceptability to patients of cystic fibrosis carrier testing offered in pregnancy by the GP. *J Med Genet* 1997;**34**:459-64.
17 Mennie ME, Gilfillan A, Compton M, Curtis L, Liston WA, Pullen I, Whyte DA, Brock DJH. Prenatal screening for cystic fibrosis. *Lancet* 1992;**340**:214-16.
18 Clausen H, Brandt NJ, Schwartz M, Skovby F. Psychological and social impact of carrier screening for cystic fibrosis among pregnant woman - a pilot study. *Clin Genet* 1996;**49**: 200-5.
19 Wald NJ, George LM, Wald NM, Mackenzie I. Couple screening for cystic fibrosis. *Lancet* 1993;**342**:1307-8.
20 Raeburn JA. Screening for carriers of cystic fibrosis. Screening before pregnancy is needed. *BMJ* 1994;**309**:1428-9.
21 Honnor M, Zubrick SR, Walpole I, Bower C, Goldblatt J. Population screening for cystic fibrosis in Western Australia: community response. *Am J Med Genet* 2000; **93**:198-204.
22 Rosenstock IM. Why people use health services. *Milbank Mem Fund Q* 1966;**44**:94-127.
23 Janz NK, Becker MH. The Health Belief Model: a decade later. *Health Educ Q* 1984;**11**:1-47.
24 Wallston KA, Wallston BS, DeVellis R. Development of the Multidimensional Health Locus of Control (MHLC) Scales. *Health Educ Monogr* 1978;**6**:160-0.

25 SPSS Inc. *SPSS release 7.5.2.* Chicago, 1997.
26 Statistics Netherlands. *Statistical yearbook* (in Dutch). The Hague: Sdu/publishers, 1998.
27 Bernhardt BA, Chase GA, Faden RR, Geller G, Hofman KJ, Tambor ES, Holtzman NA. Educating patients about cystic fibrosis carrier screening in a primary care setting. *Arch Fam Med* 1996;**5**:336-40.
28 Healthcare Marketing and Research. *Cystic fibrosis. Omnibusonderzoek onder de Nederlandse bevolking en een telefonisch onderzoek onder huisartsen en kinderartsen* (in Dutch). Bussum: Jan Schipper Compagnie, 1998.
29 Becker MH, Kaback MM, Rosenstock IM, Ruth MV. Some influences on public participation in a genetic screening program. *J Commun Health* 1975;**1**:3-14.
30 Fang CY, Dunkel-Schetter C, Tatsugawa ZH, Fox MA, Bass HN, Crandall BF, Grody WW. Attitudes toward genetic carrier screening for cystic fibrosis among pregnant women: the role of health beliefs and avoidant coping style. *Womens Health* 1997;**3**:31-51.
31 Marteau TM, Kidd J, Cook R, Michie S, Johnston M, Slack J, Shaw RW. Perceived risk not actual risk predicts uptake for amniocentesis. *Br J Obstet Gynaecol* 1991;**98**:282-6.
32 Wake SA, Rogers CJ, Colley PW, Hieatt EA, Jenner CF, Turner GM. Cystic fibrosis carrier screening in two New South Wales country towns. *Med J Aust* 1996;**164**:471-4.
33 Marteau TM, Dundas R, Axworthy D. Long-term cognitive and emotional impact of genetic testing for carriers of cystic fibrosis: the effects of test result and gender. *Health Psychol* 1997;**16**:51-62.
34 Evers-Kiebooms G, Denayer L, Welkenhuysen M, Cassiman JJ, Van den Berghe H. A stigmatizing effect of the carrier status for cystic fibrosis? *Clin Genet* 1994;**46**:336-43.
35 Livingstone J, Axton RA, Mennie M, Gilfillan A, Brock DJ. A preliminary trial of couple screening for cystic fibrosis: designing an appropriate information leaflet. *Clin Genet* 1993;**43**:57-62.
36 Schwartz M, Brandt NJ, Skovby F. Screening for carriers of cystic fibrosis among pregnant women: a pilot study. *Eur J Hum Genet* 1993;**1**:239-44.
37 Marteau TM. Population screening for cystic fibrosis: a research agenda for the next 10 years. *Am J Med Genet* 2000;**93**:205-6.
38 Schmidtke J. Proceed with much more caution. *Hum Genet* 1994;**94**:25-7.
39 Kessler RC, House JS, Anspach RR, Williams DR. Social psychology and health. In: Cook KS, Fine GA, House JS, eds. *Sociological perspectives on social psychology*. Boston: Allyn and Bacon, 1995:548-70.
40 Van de Laar J, Ten Kate LP. Preconception screening for carrier state in cystic fibrosis; testing against Health Council's criteria for genetic screening (in Dutch). *Ned Tijdschr Geneeskd* 1996;**140**:487-91.
41 Kaplan F. Tay-Sachs disease carrier screening: a model for prevention of genetic disease. *Genet Test* 1998;**2**:271-92.
42 Modell M, Wonke B, Anionwu E, Khan M, Tai SS, Lloyd M, Modell B. A multidisciplinary approach for improving services in primary care: randomised controlled trial of screening for haemoglobin disorders. *BMJ* 1998;**317**:788-91.
43 Cao A, Saba L, Galanello R, Rosatelli MC. Molecular diagnosis and carrier screening for β thalassemia. *JAMA* 1997; **278**:1273-7.
44 Standing Medical Advisory Committee. *Report of a working party of the Standing Medical Advisory Committee on Sickle Cell, Thalassemia and Other Hemoglobinopathies.* London: Her Majesty's Stationary Office, 1994.
45 Modell B, Petrou M, Layton M, Varnavides L, Slater C, Ward RHT, Rodeck C, Nicolaides K, Gibbons S, Fitches A, Old J. Audit of prenatal diagnosis for haemoglobin disorders in the United Kingdom: the first 20 years. *BMJ* 1997;**315**:779-84.
46 Neuenschwander H, Modell B. Audit of process of antenatal screening for sickle cell disorders at a north London hospital. *BMJ* 1997;**315**:784-5.
47 Burnett L, Proos AL, Chesher D, Howell VM, Longo L, Tedeschi V, Yang VA, Siafakas N, Turner G. The Tay-Sachs disease prevention program in Australia: Sydney pilot study. *Med J Aust* 1995;**163**:298-300.
48 Abeliovich D, Quint A, Weinberg N, Verchezon G, Lerer I, Ekstein J, Rubinstein E. Cystic fibrosis heterozygote screening in the Orthodox Community of Ashkenazi Jews: the Dor Yesharim approach and heterozygote frequency. *Eur J Hum Genet* 1996;**4**:338-41.

Functional characterisation of mitochondrial $tRNA^{Tyr}$ mutation (5877G→A) associated with familial chronic progressive external ophthalmoplegia

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J Med Genet 2001;**38**:703–705

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EDITOR—Chronic progressive external ophthalmoplegia (CPEO) is a common clinical manifestation of mitochondrial cytopathies characterised by ophthalmoplegia and ptosis.[1] Approximately two-thirds of CPEO patients harbour a large, heteroplasmic, mitochondrial DNA (mtDNA) deletion.[2] Some other CPEO patients carry a point mutation in the mitochondrial tRNA genes. Twelve point mutations in six mitochondrial tRNA genes have been reported to date in association with CPEO (Mitomap at http://www.gen.emory.edu/mitomap.html). Among the 12 mutations, 5703C→T in the $tRNA^{Asn}$ gene has been functionally characterised.[3] Here we report functional analysis of 5877G→A in $tRNA^{Tyr}$ identified in a patient with CPEO[4] using ρ^0 cells that lack mtDNA.

A 45 year old woman had moderate degrees of ptosis, external ophthalmoplegia, and proximal muscle weakness from the age of 28. She had no sensorineural hearing loss, ataxia, pigmentary retinopathy, hypogonadism, or mental retardation. She had episodic diarrhoea of unknown aetiology. An ECG showed atrioventricular conduction block, while EEG, brain CT, and brain MRI showed no abnormalities. An exercise loading test of 15 watts for 15 minutes on a bicycle ergometer[5] raised her serum lactate from 6.9 mg/dl to 24.0 mg/dl (normal, less than 18.0 mg/dl), and her serum pyruvate from 0.6 mg/dl to 1.4 mg/dl (normal, less than 1.3 mg/dl), thereby increasing the lactate to pyruvate ratio from 10.7 to 17.1 (normal, less than 13.8). A biopsy specimen obtained from the biceps brachii showed 4.0% ragged red fibres and 0.7% cytochrome *c* oxidase negative fibres.

Mutation analysis of muscle mtDNA was briefly described previously (patient 2 in Ozawa *et al*[4]). Determination of the entire mtDNA sequence showed 34 nucleotide changes; 33 were homoplasmic and were observed in 274 controls with variable frequencies. A 5877G→A transition in the $tRNA^{Tyr}$ gene was heteroplasmic and unique to the patient. The ratios of mutant to wild type mtDNA were 73% in skeletal muscle and 0.7% in blood (fig 1B). The 5877G→A mutation is located in the DHU loop of the $tRNA^{Tyr}$ gene (fig 1A). The 5877G base pairs with 5905C in the variable loop (circle in fig 1A) to form the L shaped tertiary structure of the tRNA