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Perceptions of risk and predictive testing held by the first degree relatives of patients with rheumatoid arthritis in England, Austria and Germany: a qualitative study

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Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups

Table 1
Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No	Item	Guide questions/description	
Domain 1: Research team and reflexivity			
Personal Characteristics			
1.	Interviewer /facilitator	Which author/s conducted the interview or focus group?	RJS, KK, ME, AH, MS, EM
2.	Credentials	What were the researcher's credentials? *E.g. PhD, MD*	RJS, KK, ME, AH, MS highest qualifications are PhD, EM highest qualification is MSc
3.	Occupation	What was their occupation at the time of the study?	RJS, KK, ME, MS, EM are research fellows AH is a rheumatologist
4.	Gender	Was the researcher male or female?	Mixture of male and female
5.	Experience and training	What experience or training did the researcher have?	All have extensive experience and training
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	Invitation letters were sent, participants were spoken to over the phone and before the interview commenced participants were given an overview of the research study.
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*	Participants were given participant information sheets, and given a verbal introduction to the study, its aims and the procedure.
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons*	The interviewers were from a range of backgrounds including medicine, psychology and social

No	Item	Guide questions/description	
		and interests in the research topic	sciences.
Domain 2: study design			
Theoretical framework			
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	Yes, thematic analysis
Participant selection			
10.	Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	Convenience
11.	Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	Mail
12.	Sample size	How many participants were in the study?	34
13.	Non-participation	How many people refused to participate or dropped out? Reasons?	None participation rates across the centres were problematic to calculate accurately. Main reasons for not participating were difficulties in arranging suitable times and locations for interviews.
Setting			
14.	Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	Clinical and academic settings.
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?	Interviews were conducted on a one-to-one basis.
16.	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	The characteristics of the sample are presented in the tables contained within the paper
Data collection			
17.	Interview guide	Were questions, prompts,	Yes, the interviews were

No	Item	Guide questions/description	
		guides provided by the authors? Was it pilot tested?	semi-structured
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?	No
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	Digital audio recorders were used.
20.	Field notes	Were field notes made during and/or after the interview or focus group?	No
21.	Duration	What was the duration of the interviews or focus group?	60-90 minutes
22.	Data saturation	Was data saturation discussed?	Yes, thematic saturations was achieved.
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	An interactive feedback process was used were transcripts were reflected and commented upon, however, transcripts were not feedback to participants for correct.
Domain 3: analysis and findingsz			
Data analysis			
24.	Number of data coders	How many data coders coded the data?	Five
25.	Description of the coding tree	Did authors provide a description of the coding tree?	No, instead major themes were identified.
26.	Derivation of themes	Were themes identified in advance or derived from the data?	Themes were derived from the data
27.	Software	What software, if applicable, was used to manage the data?	NVIVO
28.	Participant checking	Did participants provide feedback on the findings?	No
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g.*	Yes, see tables 2, 3 and 4.

No	Item	Guide questions/description	
		participant number	
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
31.	Clarity of major themes	Were major themes clearly presented in the findings?	Yes, major themes were identified.
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes

Title: Perceptions of risk and predictive testing held by the first degree relatives of patients with rheumatoid arthritis in England, Austria and Germany: a qualitative study

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Keywords

Risk, Rheumatoid Arthritis, First-degree Relatives, Predictive testing, Qualitative

Abstract

Objectives: The family members of rheumatoid arthritis (RA) patients are at increased risk of developing RA and are potential candidates for predictive testing. This study explored the perceptions of first degree relatives of people with RA about being at risk of RA and engaging in predictive testing.

Methods: Thirty-four first-degree relatives (siblings and off-spring) of patients with RA from the UK, Germany and Austria participated in semi-structured interviews about their perceptions of RA risk and the prospect of predictive testing. Interviews were audio-recorded, transcribed verbatim and analysed using thematic analysis.

Results: First-degree relatives were aware of their susceptibility to RA, but were unsure of the extent of their risk. When considering their future risk, some relatives were concerned about the potential impact that RA would have on their lives. Relatives were concerned that knowing their actual risk would increase their anxiety and would impact decisions about their future. Also, relatives were concerned about the levels of uncertainty associated with predictive testing. Those in favour of knowing their future risk felt that they would need additional support to understand the risk information and cope with the emotional impact of this information.

Conclusions: Identifying individuals at risk of RA may allow targeted interventions to reduce the risk and consequence of future disease; however, relatives have concerns about predictive testing and risk information. The development of strategies to quantify and communicate risk needs to take these views into account and incorporate approaches to mitigate concerns and minimize the psychological impact of risk information.

Strengths and limitations

- This study used inductive qualitative interviews to explore perceptions about risk and predictive testing in the first-degree relatives of people with RA.
- This study identified positive and negative perspectives surrounding predictive testing, and why some people at risk may not wish to be tested.

- Further research is needed to quantify the numbers of people at risk holding negative perceptions about predictive testing, and identify the behavioural implications of these beliefs.
- Communicating risk information to relatives effectively while reducing the psychological burden associated with this information, should be the focus of future interventional research.

Funding statement

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Competing interests

The authors have no conflicts of interests to declare.

Contribution statement

All authors made a substantial contribution to study conception and design. RJS, MS, ME, EM, KK collected the data. RJS analysed and interpreted data. All authors were involved in drafting the article, revising it and final approval of the version of the article to be published was given by all authors.

Introduction

Rheumatoid arthritis (RA) is a chronic destructive polyarthritis. It affects approximately 1% of the population [1] and typically manifests in the 4th and 5th decades of life.[2-4] Delays in diagnosis and treatment of RA are common and are associated with worse outcomes.[5-8] Recently, an increased research effort has been directed towards the 'at risk' phases of RA, prior to the development of clinical signs of joint swelling, to identify those at risk of developing RA and to reduce this risk through the modification of environmental risk factors and pharmacological intervention.[9;9-11]

Genetic factors contribute significantly to the risk of RA.[12] For seropositive RA at least half of the risk is conferred by genetic risk factors [13] with recent large genetic studies having identified over 100 susceptibility loci.[14;15] Population based epidemiological studies have shown that having a family history of RA increases the risk of RA by approximately 3-5 times,[16-18] with the risk being higher in first degree relatives than second degree relatives.[17] Furthermore, a range of environmental and life-style risk factors including occupational exposure to pollutants,[19] body mass index,[20] periodontitis,[21] reproductive factors,[22] smoking,[23] and dietary factors[24-26] contribute to the increased risk of developing RA. Some of these environmental risk factors may interact mechanistically with genetic risk factors to increase the risk of RA,[27] and others may have familial associations thus contributing to the familial aggregation of RA.[28;29]

Individuals with genetic and environmental risk factors for RA may progress through a phase associated with the development of systemic autoimmunity (e.g. the development of autoantibodies such as rheumatoid factor,[30;31] anti–citrullinated protein / peptide antibodies and anti-carbamylated protein antibodies[32]) before the clinical symptoms and signs of RA manifest.[9] It remains unclear whether there are changes detectable within the synovium during the phase of autoantibody positivity prior to the development of joint swelling.[33;34]

Together these data suggest that information related to genotype, environmental exposures and measures of autoimmunity and inflammation may be used to predict RA development in individuals who have not yet developed clinical disease. A potential target population for

such testing, with a view to risk stratification and intervention to modulate risk, are the first-degree relatives of individuals with RA. Indeed a number of ongoing prospective studies are recruiting the first-degree relatives of patients with RA to study disease mechanisms driving the switch to RA,[35] to develop predictive algorithms for RA, and to test interventions to reduce RA risk.[36] Whilst considerable research effort is thus focussed on the first-degree relatives of RA patients, and a qualitative study has gathered data relating to their views of preventive strategies,[37] little is known about how such individuals view issues related to their susceptibility to and risk of developing RA, and how willing they would be to be assessed and tested to have this risk quantified. The present qualitative study addresses these issues.

Methods

Ethical approval was obtained in the UK from the HumberBridge National Research Ethics Committee, in Austria from the Ethics Committee of the Medical University of Vienna and in Germany from the Ethics committee of the University of Erlangen-Nuremberg.

Procedure

Eligible participants were the first-degree relatives (offspring and siblings) of people with RA. Participants were required to be at least 18 years of age and without a diagnosis of inflammatory joint disease.

Patients with RA were approached during routine secondary care clinics in Birmingham (United Kingdom), Erlangen (Germany) and Vienna (Austria) and were given a letter to pass on to a first-degree relative of their choosing inviting them to participate in an interview about risk and predictive testing for RA. Participants were recruited between October 2014 and October 2015. It was explained to patients that it was entirely at their discretion whether to pass on the invitation letter. All research participants (i.e. the participating first-degree relatives) gave written informed consent prior to interview.

The semi-structured interviews were guided by an interview schedule which was informed by a review of the qualitative literature exploring perceptions of risk and testing in those at risk of developing a chronic disease.[38;39] The interviews aimed to assess personal perceptions of risk, therefore, one-to-one interviews were conducted. In addition, an international multi-disciplinary team of healthcare professionals, patient research partners and researchers working on the EuroTEAM project (www.team-arthritis.eu) reviewed and redrafted the interview schedule (see table 1 for sample questions from the final interview schedule).

One-to-one Interviews were conducted at local hospitals or by telephone (for those participants who had difficulty in attending the hospital for a face-to-face interview). Interviews lasted between 30 and 90 minutes and were digitally audio-recorded. In the UK, participants who wanted further information about arthritis were advised to contact Arthritis Research UK, the National Rheumatoid Arthritis Society or the local hospital's Patient Advice and Liaison Service. Participants in Austria and Germany were advised to contact the local rheumatology outpatient clinic.

The interviews were transcribed verbatim. Interviews conducted in German were translated into English following transcription. Transcripts were anonymised and analysed centrally in Birmingham, UK, by RJS.

Analysis procedure

Data collection and analysis were carried out in parallel to assess when thematic saturation of major developing themes had been achieved. The data were analysed using a thematic approach[40] facilitated by NVivo (a qualitative software programme).[41] Transcripts were subjected to line-by-line coding by RJS. Patient research partners blind coded three transcripts to develop reliable and inclusive themes informed by multiple perspectives. Discussion of the coding framework took place between researchers and patient research partners. Coding categories that lacked concordance were discussed and absorbed into the coding framework. The initial codes were then grouped into the most noteworthy and frequently occurring categories. The core themes extracted and presented here focus on

perceptions of first-degree relatives about their personal risk of RA and their views on being tested.

Results

Thirty-four first-degree relatives of patients with RA participated, 24 from the UK, 3 from Germany and 7 from Austria. Six participants were siblings of an RA patient, 26 were the adult offspring an RA patient and 2 participants had both a sibling and a parent with RA. Participants were aged between 23 and 67 years (mean 39 years) and 26 (76%) were female (see table 2 for participant characteristics). Quotations are presented in tables 3, 4, 5 and 6 and are referred to in the text using "Q" followed by the quotation code.

Understanding of family history and genetic factors as risk factors for RA

The first-degree relatives of people with RA understood that there was a hereditary component to RA (Q1), and often used the word "genetic" to describe the cause of their increased risk (Q2). First-degree relatives (from here on referred to as "relatives") recognised that they were more susceptible to developing RA than second-degree relatives (Q3). Interestingly, some felt that they were more susceptible to developing RA than other first-degree relatives because they appeared to follow other patterns of illness displayed by their relative with RA (Q4). Additional biological factors, such as being female and some environmental factors were also described as playing a role in the development of RA (Q2&5).

When considering their perceived personal susceptibility, relatives reported that there were aspects of familial risk, particularly genetic susceptibility, which they found difficult to understand. One relative felt that effectively communicating an understanding of genetic risk to the public was extremely challenging (Q6). Others felt that they needed more information about their level of risk as a relative and the specific role that genes associated with RA played in this risk (Q7).

When considering their susceptibility to RA, relatives voiced their concerns about the future, and how being at risk of developing RA was a worry for them. Those who had considered their personal susceptibility to RA, described being fearful of what they may uncover if they were to have their risk quantified. For some, the prospect of living with RA would entail great amounts of uncertainty (Q8). For many, having witnessed the impact of RA on their sibling / parent, heightened the worry they felt in relation to the possibility of developing RA themselves in the future (Q9). Interestingly, a small number of relatives had experienced joint related symptoms but had not yet sought medical advice, being fearful of the potential outcome (Q10).

Personal considerations of RA risk and communication about risk within families

Relatives discussed knowing little about RA or its risk factors, feeling that they had been "shielded" or "protected" from this knowledge by their sibling / parent (Q11). Also, relatives described how they rarely discussed RA within their family unit, and in some cases the invitation to participate in this study was the first time that the opportunity to discuss RA, and its risk had emerged (Q12). For one relative, receiving the invitation to take part in this study facilitated the first conversation he had had with his father about RA (Q13). Another described how his mother had had some concerns about him taking part in this study, because of the worry which discussing issues surrounding risk and predictive testing may cause (Q14). One relative described how her brother had been asked to take part in this study, but ignored the request; her mother had then approached her and encouraged her to participate (Q15). This relative suggested that it was her attitude towards health which set her apart from her brother.

Most relatives had not fully considered issues related to their personal susceptibility to RA prior to being approached to take part in this study (Q16). Some relatives indicated that taking part in this study had been a positive experience for them and had provided them with much needed knowledge, a chance for reflection on their risk and a greater understanding of RA and how it affected their sibling / parent (Q17). However, others described how they would prefer to avoid considering their personal risk of RA to avoid experiencing worry or anxiety about the future (Q18).

Perceptions surrounding the use of predictive tests: positive perspectives

Most relatives were in favour of the basic principle behind predictive testing - identifying those at risk and quantifying the level of risk (Q19). It was also felt that the information gained from predictive testing could be acted upon to reduce the future risk of developing RA (Q20). In particular, relatives recognised the importance of early intervention, and were aware that testing could put them "on alert" for the early symptoms of RA (Q21), or suggested that they might be able to take preventive treatment (Q22). Many relatives felt that it was important to know that they were at risk, and that information related to their actual risk would be of value to them, allowing them to "mentally" prepare for the future (Q23). Others could see the benefit of preparing for the functional limitations that may be associated with RA (Q24). A few had already undertaken predictive testing to explore their personal risk of developing RA (Q25). Some were willing to be tested for altruistic reasons such as taking part in research (Q26).

Perceptions surrounding the use of predictive tests: negative perspectives

The ability of predictive tests to quantify risk was widely discussed (Q27), with one participant questioning the specificity and sensitivity of the test (Q28). Relatives expressed a desire for tests that would, with a very high likelihood, be able to confirm or exclude the fact that they would develop RA (Q29). However, many relatives suspected that test results would give them an intermediate risk of developing RA and others highlighted concerns about "false positive" results (Q30). Some believed that predictive testing would not be able to give them answers to questions they thought were important for example how severe would their RA be were they to develop it, and when it would be most likely to begin (Q31).

Relatives were worried about the impact of testing on their family members and in particular on their sibling / parent with RA (Q32). Participants felt that by seeking information about risk and pursuing testing that they would cause their relative with RA to experience stress, worry or feelings of guilt. Participants were further worried about the stress that predictive test results may cause them. One even suggested that such stress could cause the disease to develop earlier than it otherwise would (Q33).

Relatives felt that being given risk information when they were young would be a particular burden (Q34). Instead, they felt that testing should be left until later in life, when the chance of developing a condition like RA was higher. Risk information was considered to have significant implications for future life choices and could make them "rush" though life (Q35). One relative suggested such information could bring forward major life decisions, such as having children (Q36).

Some relatives reflected upon previous negative personal experiences of having received poorly communicated test related information (Q37). For some, the approach to the delivery of risk information represented an important feature of a predictive test, and may determine whether the test would be acceptable to them. Relatives discussed how they would want to be told prior to the test what format the result would take. Some suggested that they would like to receive the results by letter, and then be given the opportunity to discuss the results with a healthcare professional (Q38). Other relatives emphasized the importance of talking to someone about the test result, especially to manage the psychological distress that may be associated with receiving a "positive" test result (Q39). Many relatives felt that there was a need for ongoing support from a healthcare professional following testing (Q40).

Discussion

This study explored the degree to which first-degree relatives of people with RA felt that they were susceptible to developing RA and their perceptions of predictive testing. Most relatives were aware that there was a genetic contribution to the risk of RA, and that they may be susceptible to developing RA; however they were unsure of the extent of the additional risk. Relatives highlighted the need for additional information about familial risk and described the need for better communication strategies in relation to imparting this information.

Generally, first-degree relatives felt that there was a need for more information and support specifically designed for the family members of people with RA. The current lack of support and information was suggested to have a number of effects, including family members not feeling able to communicate and support the person affected with RA and not feeling able to understand concepts surrounding the nature of RA and the risks associated with RA. Studies of information sharing amongst family members at risk of cancer have found that patients with the disease do not always communicate risk information in a timely or thorough fashion.[42] Forrest et al found that relatives from smaller families, and female relatives were more likely to make contact with genetic services.[43] Research has shown that genetic counselling can facilitate interfamily communication, and can help to minimize distress and increase the number of family members making contract with health services to be tested.[44;45]

An incidental finding of this research was that being invited to take part in research about risk was the first time that some relatives had fully considered their personal susceptibility to RA. In some cases this exposure was viewed positively but in other cases it caused worry and concern. It is difficult to draw conclusions about the specific impact taking part in this study had on relatives' well-being but we note that relatives did indicate that support mechanisms would be helpful to enable them to understand and cope with risk related information, especially if predictive testing were to be offered. We would suggest that

researchers accessing participants in "at risk" populations pay particular attention to the impact that an invitation to participate and participation itself may have, and offer additional support to mitigate against anxiety caused. While personal susceptibility may not have been considered, perceptions of RA severity may predict personal willingness to engage in predictive testing. It is possible that first degree relatives of people with more severe forms of RA or poorly controlled disease maybe more motivated to engage in predictive testing. This would be in line with the predictions of the health belief model.[46] A quantitative investigation to assess the effect of factors such as disease severity in people with RA, on their family members' perceptions of risk and orientation towards predictive testing is needed to test this hypothesis.

In addition, it became apparent during the course of this study that some relatives were symptomatic but had not yet sought medical help. Detailed information on the health status of the participating relatives was not gathered within this study but those who were symptomatic were advised to speak to their family physician, and were given details of resources for obtaining additional information. However, the symptomatic nature of some relatives raises important issues surrounding informing relatives about risk, and the importance of seeking help quickly should symptoms emerge. While some relatives were aware that their symptoms may be indicative of the early stages of RA, and were worried about what information would be revealed to them if they sought help, few were aware of the importance of early intervention. Were information about the benefits of early intervention in preventing joint destruction made available to them, it is possible that their attitude to help seeking may have been different.

This study has a number of limitations. Firstly, our access to first-degree relatives was via patients with RA. Some relatives described how they were chosen in preference to other relatives, who would either worry too much or not be receptive to discussing issues related to risk. The findings presented here may thus not fully reflect the range of views related to risk and testing held by first-degree relatives. This potential limitation highlights the need to fully understand the barriers that patients with RA face when discussing issues of risk with family members. A second limitation of this research was that the majority of participants were female. A criticism of many qualitative studies in the field of RA is that the male

perspective is underrepresented.[8] While the female: male ratio of RA is typically 2:1 it is essential that studies attempt to include the views of more male participants. Therefore, we acknowledge that themes related to gender and male perspectives of risk and predictive testing did not reach saturation and are not represented in our data. A final limitation is that only a small number of individuals from ethnic-minority communities were interviewed, therefore, a full understanding of the cultural barriers to predictive testing was not achieved.

Besides these limitations, this study has a number of strengths. Relatives were sampled from centres in 3 different European countries and saturation of the main themes was achieved by combining interview data from all centres; furthermore, no differences in the views expressed by relatives sampled from different European countries were detected. Gathering data from multiple countries means that interventions developed based on these data are likely to be relevant in multiple contexts. A further strength of this study was the support given by an international panel of patient research partners who advised researchers and acted as co-researchers.

Identifying individuals at risk of RA may allow targeted interventions to reduce the risk and consequence of future disease; however, our data show that relatives have concerns about predictive testing and risk information that would result from it (the key messages of this study are summarised in tabled 7). The future development of strategies to quantify and communicate risk needs to take these views into account and incorporate approaches to mitigate concerns and minimize any negative psychological impact of risk information.

Data Sharing Statement

Unpublished data is available in the form of unanalysed interview transcripts sorted in an NVIVO file from the corresponding author. Data can be obtained by emailing the corresponding author.

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Table 1: Sample interview schedule for those at risk of developing RA

- Tell me what you know about RA?

PROMPTS: What do you think the causes of RA could be? What do you think the risks factors for RA are? Tell me about how serious you think RA is? How would you know you had RA e.g what symptoms would you expect? What would be the impact of RA on your life? Do you think you would be able to control RA yourself? Do you think there are treatments available that would effectively treat RA?

- Do you ever worry about the possibility of developing RA in the future?
- What would you think if you were told that you could have a test that would tell you how likely you were to develop RA?

PROMPTS: What sort of information should this test give you? When do you think would be the right time to get this information? How would you feel about the idea of having a test that would tell you your chance of developing RA in the future? In what ways do you think it would be helpful for you to know your chances of developing RA?

- What would your concerns be if you knew what your risk of developing RA was?
- What kind of tests do you think people might be able to do to work out whether or not you might develop RA (test that are available now and tests that might become available in the future)?

Table 2: Details of first degree relatives of RA patients who participated in the interviews

Participant no.	Gender	Age	Ethnicity	Relation to RA patient	Experience of testing	Self-reported musculoskeletal symptoms	Interview country
Participant 1	Female	36	White British	Daughter	None	None	UK
Participant 2	Female	42	White British	Daughter	None	Previous septic arthritis	UK
Participant 3	Male	35	White British	Son	None	None	UK
Participant 4	Male	67	White British	Brother	None	None	UK
Participant 5	Male	31	White British	Son	Reports having had a "genetic test" for RA (performed by family physician).	None	UK
Participant 6	Female	23	White British	Daughter	None	None	UK
Participant 7	Female	30	White British	Daughter	None	Ankle pain and intermittent ankle swelling attributed by patient to a previous "ankle dislocation"	UK
Participant 8	Female	39	White British	Daughter	Rheumatoid factor	Elbow pain	UK

					previously measured		
Participant 9	Female	54	White British	Sister	None	Finger pain	UK
Participant 10	Female	35	White British	Daughter	None	"Inflamed knee" during pregnancy	UK
Participant 11	Female	44	White British	Sister AND Daughter	None	Back pain	UK
Participant 12	Female	44	White British	Sister	None	Finger pain	UK
Participant 13	Female	41	White British	Sister AND Daughter	Rheumatoid factor previously measured by family physician	Finger pain, stiffness and swelling	UK
Participant 14	Female	60	White	Daughter	Has had "blood tests" (participant unsure which)	Has a diagnosis of osteoarthritis	UK
Participant 15	Female	29	White British	Daughter	None	None	UK

Participant 16	Female	40	White British	Daughter	None	None	UK
Participant 17	Female	41	Asian (UK born)	Daughter	None	None	UK
Participant 18	Female	28	White British	Daughter	None	None	UK
Participant 19	Male	42	Chinese	Son	None	None	UK
Participant 20	Female	25	White British	Daughter	None	None	UK
Participant 21	Female	41	White British	Daughter	None	Had previous joint swelling in wrists and hands	UK
Participant 22	Female	32	White British	Sister	None	None	UK
Participant 23	Female	44	White British	Daughter	None	None	UK
Participant 24	Male	47	White British	Son	None	None	UK
Participant 25	Female	29	White German	Daughter	None	None	Germany

Participant 26	Female	37	White German	Daughter	None	None	Germany
Participant 27	Female	51	White German	Daughter	None	None	Germany
Participant 28	Female	21	White Austrian	Daughter	None	None	Austria
Participant 29	Male	33	White Austrian	Son	None	None	Austria
Participant 30	Female	65	White Austrian	Sister	None	None	Austria
Participant 31	Female	36	White Austrian	Sister	Reports having had a blood test	None	Austria
Participant 32	Male	37	White Austrian	Son	None	None	Austria
Participant 33	Male	37	White Austrian	Son	None	None	Austria
Participant 34	Female	33	White Austrian	Daughter	None	None	Austria

Table 3 Quotations related to an understanding of family history and genetic factors as risk factors for rheumatoid arthritis

Code	Quotation
Q1	*"I see that my mother has it and I'm just worried that it might be passed on to me or my sister or other members of my family." (Participant 19)*
Q2	*"In my opinion it's environmental factors or genetics." (Participant 28)*
Q3	*"So I know it's blood-related... I think if it was your cousin or your aunt there'd be a slim chance….. being direct blood-related, I would class myself as, or think of myself that I am at a higher risk than most."(Participant 6)*
Q4	*"I seem to follow my mum in absolutely everything, like my brother and sister they're quite like my dad, they never get ill, they never catch a cold. Whereas if there's a cold going around I will get it and the same with my mum… So I was a bit like 'oh, maybe I'll get it'." (Participant 18)*
Q5	*"I know that there's a genetic tendency. That it runs in families. I'm female, so I'm more at risk because I'm female… I know first degree relative increases your risk, so yeah, it does worry me." (Participant 10)*
Q6	*"Genetics really worry me because I don't know anything about them and I think when people think of genetics they think of like I don't know it's quite like a complicated thing that we're never going to understand because there's no simple way of putting it….. But like your average Joe Bloggs [average person] isn't going to know extensive information about your genes." (Participant 20)*
Q7	*"For me personally it's kind of hard facts and figures; I'm more comfortable knowing in terms of percentages. I know my dad has got rheumatoid arthritis, and if you've got a hard fact and figure to say that the chances of a close relative, son or daughter, developing rheumatoid arthritis at some point in their life then that information would be useful to me." (Participant 5)*
Q8	*"It [life] wouldn't be predictable anymore; I wouldn't know how things would be from one day to the next, or in an hour's time, when I woke up the next morning, wondering what the day would bring. I think it's pretty serious, it restricts your everyday life. And it differs – my father has pain and sometimes it's there,*

	sometimes it's not; it's unpredictable." (Participant 25)
Q9	*"I do worry about it, yeah, because I don't want to end up developing anything like that. I like to keep busy and I don't want to be restricted. It is a big worry, yeah. I don't want to go through what my mum's going through at the moment, because she's been through a lot." (Participant 13)*
Q10	*"I've got pain down my left leg [okay], but I just don't know whether it's sciatica, or whether it could be something linked to arthritis, but I'm too frightened to go and have a scan. So I probably do need it to find that. I'm just putting it off." (Participant 15)*

Table 4 Quotation related to personal considerations of rheumatoid arthritis risk and communication about risk within families

Code	Quotation
Q11	*"That's exactly what he doesn't talk to me about, he's the kind of person who leaves others out of it, deals with it by himself." (Participant 30)*
Q12	*"I am worried about that….I was quite surprised when mum said that she'd had this letter explaining about the research that you're doing." (Participant 23)*
Q13	*"He doesn't tend to talk about it. He didn't want to ask me to do this phone call, but forced himself to one day…This is probably the first time he's actually asked me to do anything and he was clearly uncomfortable." (Participant 24)*
Q14	*"I never had that information of what happens, how you're made at higher risk, I've never had that in like black and white ….which makes me think she doesn't know or maybe she's just trying to protect me like a mother does. Because I think she was quite worried about me taking part….she's quite worried about what I'd find out. (Participant 5)*
Q15	*"My mum, sort of, mentioned this to him [brother], and he was just, like, ignored the fact that she'd said anything to me. And then she came to me and said, 'I thought I'd ask your brother first but he won't,' and I said, 'I don't mind,' but he's probably different to me, just blissful ignorance, whereas I'm probably a little bit different." (Participant 2)*
Q16	*"Up until now I have never thought about it, what that would be like, whether it might happen" (Participant 28)*
Q17	*"I guess before we spoke I couldn't understand what it was exactly that was making her finger sore or swollen or anything like that. I would just be like, drink more milk." (Participant 20)*
Q18	*"You only worry too much and rack your brain, because then I have to consider that my children could get it too and then you would worry too much. It's more comfortable to avoid it." (Participant 32,)*

Table 5 Quotations related to perceptions surrounding the use of predictive tests: positive perspectives

Code	Quotation
Q19	*"I'm open to everything, well, I don't know why I shouldn't have that done, I couldn't think of a reason off the top of my head not to do it." (Participant 31)*
Q20	*"If I was offered a test, I'd be very happy to have one. I don't need to think about that. Well, it might be if it might help me combat a disease later, or at least know how to treat it. Well, if I'm at risk I think it would be helpful to know." (Participant 3)*
Q21	*"I would do that straight away, because I want to know as soon as possible, because I think the more you know the earlier, the more you can do about it." (Participant 31)*
Q22	*"I think that with kind of information, I'd be more keen to, sort of, sort out what I needed to do to try and prevent that becoming a problem. If I could take some sort of medication to…head it off before it became a big problem." (Participant 2)*
Q23	*"I think that would be a good thing. I think I'd like to know because then I may be able to prepare a bit more, like mentally as well." (Participant 20)*
Q24	*"Yes, it would. I think I would have the test just to see what the long-term forecast is, because my job's fairly labour intensive. I'd be willing to know what the future holds, just from the point of view of my job circumstances at work." (Participant 19)*
Q25	*"Actually I did get tested, but it was a long time ago." (Participant 27)*
Q26	*"I'm not averse to having them, especially, if it helps with research and stuff like that." (Participant 2)*

Table 6 Quotations related to perceptions surrounding the use of predictive tests: negative perspectives

Code	Quotation
Q27	*"Exactly, if it is only a vague presumption where they say, yes, you could perhaps out of two to five people or something, you could get it and the others wouldn't, well that is very vague. (Participant 32)*
Q28	*"That depends on the test, how specified it is and how sensitive it is, otherwise I would not have the test done." (Participant 29)*
Q29	*"Because if told me – it's only how likely, it's not a, 'You will develop it,' and it doesn't tell you when you will develop it. So I think if somebody said to me, 'There's this test out there and it'll tell you whether you might develop it,' I wouldn't want it, because you could just live your life in fear and never actually develop it. So unless it was 100% guaranteed, and somebody could say, 'You will develop it within this time frame,' I don't wanna [want to] spend the next 30 years worrying about something, when I could be enjoying those 30 years. So, no, I'd probably – it depends on the exact details of the test. (Participant 10)*
Q30	*"Or, equally, I guess, false positive. If you've got one really bad, sort of, joint that you've tested, it could, kind of, put a bit of a negative spin on it." (Participant 1)*
Q31	*"It would be nice to know when … at what point in time you were going to get ill, and how severe it was going to be … but I don't know whether a test can find that out. (Participant 25)*
Q32	*"But I wouldn't want to worry my mum by saying, can you get me a leaflet on testing. I wouldn't want my mum to worry that I was going for this test….to know that if in five years time I'll get it, I don't want her to know that because I think that would worry her more than anything." (Participant 6)*
Q33	*"On the one hand you know that you might develop the disease and it is of course stressful, because then you know, one day, when I'm about 30 – 40 years old, it will start and then my body will become weaker and I will get this disease, then it could create a lot of stress to have these negative thoughts. I don't know what the psychological effect would be on the body, whether it really might break out*

	sooner. If you don't know, so, if you say, I don't know and you live each day as it comes, meaning that it might break out at a later date." (Participant 32)
Q34	*"From personal experience, I think it would be something that when I got a bit older and certain things started going wrong with me or I started getting more illnesses I'd think I'd need to start looking to what all these problems are. At this particular moment in time, when there's generally nothing wrong with me, I just think that I don't really need to delve too much into that sort of information."(Participant 4)*
Q35	*"Yeah I kind of wouldn't want this test to tell me that I had a 50/50 chance of getting it in the next five years because that would change my entire perception on what I wanted. And I guess if someone gave me that bit of information I'd have to seriously think, well maybe I can't have that, maybe I've got to like push everything forward like get married and have kids before I start to take medication which I guess that's a lot of information I don't know about in that if I had to start taking that medication would that affect me having kids. It's like knowing when you're going to die that doesn't sit right with me either." (Participant 15)*
Q36	*"I think, if, for argument's sake, I'd gone for the test tomorrow, and the results came back and they said, 'Yeah, you're at high risk,' and in two years' time, the symptoms kicked in, you're then thinking, 'Right, okay.' We'd probably want a second child and we'd want a third, 'Let's do it now,' sort of, thing, but otherwise, I think, you know, just life would carry on" (Participant 6,)*
Q37	*"The GP [family physician] literally just sat me down, blurted some technical words out, medical terminology to me that went straight over my head and, again, didn't sink. I think, just keep simple, instead of baffling people with medical science, really, of your technical words that you use, compared to what, sort of, the general public are going to understand." (Participant 6)*
Q38	*"I'd be happy, I think, if, before the test, someone would explain the kind of outcome to expect. And then when I got the test results back, it would be okay by post, as long as there was, kind of, accompanying information. I suppose at that point you'd probably end up going to see someone anyway to talk through what tablets or whatever you could take." (Participant 1)*

Q39	*"I suppose it would be sensible to go and talk to somebody about it. (Participant 3)*
Q40	*"I think it's a good idea to talk to somebody and find out more information. I think seeing somebody on a regular basis, like every year or something, might be good if you knew that you were going to get it. Obviously, you're going to have more and more questions, aren't you? Yeah, for an update and just to see how things are going. Obviously, as time goes on, you're going to have more questions and so I think it would be good to speak to somebody." (Participant 20)*

Table 7: Key messages

1. Identifying those at risk of RA, and quantifying their risk, may help guide targeted interventions to reduce future disease burden. This qualitative study found that first-degree relatives of people with RA, who are themselves at an enhanced risk of RA, had a number of concerns in relation to predictive testing.
2. Some relatives would be unwilling to undergo predictive testing and were worried about the psychological impact of risk information. Others were more receptive and recognized that such information could facilitate the development and implementation of preventive strategies as well as encouraging prompt help-seeking and intervention at the onset of RA symptoms.
3. Developing strategies which communicate risk information effectively while reducing the psychological burden associated with this information is essential.

Title: Perceptions of risk and predictive testing held by the first degree relatives of patients with rheumatoid arthritis in England, Austria and Germany: a qualitative study

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Keywords

Risk, Rheumatoid Arthritis, First-degree Relatives, Predictive testing, Qualitative

Abstract

Objectives: The family members of rheumatoid arthritis (RA) patients are at increased risk of developing RA and are potential candidates for predictive testing. This study explored the perceptions of first degree relatives of people with RA about being at risk of RA and engaging in predictive testing.

Methods: Thirty-four first-degree relatives (siblings and off-spring) of patients with RA from the UK, Germany and Austria participated in semi-structured interviews about their perceptions of RA risk and the prospect of predictive testing. Interviews were audio-recorded, transcribed verbatim and analysed using thematic analysis.

Results: First-degree relatives were aware of their susceptibility to RA, but were unsure of the extent of their risk. When considering their future risk, some relatives were concerned about the potential impact that RA would have on their lives. Relatives were concerned that knowing their actual risk would increase their anxiety and would impact decisions about their future. Also, relatives were concerned about the levels of uncertainty associated with predictive testing. Those in favour of knowing their future risk felt that they would need additional support to understand the risk information and cope with the emotional impact of this information.

Conclusions: Identifying individuals at risk of RA may allow targeted interventions to reduce the risk and consequence of future disease; however, relatives have concerns about predictive testing and risk information. The development of strategies to quantify and communicate risk needs to take these views into account and incorporate approaches to mitigate concerns and minimize the psychological impact of risk information.

Strengths and limitations

- This study used inductive qualitative interviews to explore perceptions about risk and predictive testing in the first-degree relatives of people with RA.
- This study identified positive and negative perspectives surrounding predictive testing, and why some people at risk may not wish to be tested.

- Further research is needed to quantify the numbers of people at risk holding negative perceptions about predictive testing, and identify the behavioural implications of these beliefs.
- Communicating risk information to relatives effectively while reducing the psychological burden associated with this information, should be the focus of future interventional research.

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Competing interests

The authors have no conflicts of interests to declare.

Contribution statement

All authors made a substantial contribution to study conception and design. RJS, MS, ME, EM, KK collected the data. RJS analysed and interpreted data. All authors were involved in drafting the article, revising it and final approval of the version of the article to be published was given by all authors.

Introduction

Rheumatoid arthritis (RA) is a chronic destructive polyarthritis. It affects approximately 1% of the population [1] and typically manifests in the 4th and 5th decades of life.[2-4] Delays in diagnosis and treatment of RA are common and are associated with worse outcomes.[5-8] Recently, an increased research effort has been directed towards the 'at risk' phases of RA, prior to the development of clinical signs of joint swelling, to identify those at risk of developing RA and to reduce this risk through the modification of environmental risk factors and pharmacological intervention.[9;9-11]

Genetic factors contribute significantly to the risk of RA.[12] For seropositive RA at least half of the risk is conferred by genetic risk factors [13] with recent large genetic studies having identified over 100 susceptibility loci.[14;15] Population based epidemiological studies have shown that having a family history of RA increases the risk of RA by approximately 3-5 times,[16-18] with the risk being higher in first degree relatives than second degree relatives.[17] Furthermore, a range of environmental and life-style risk factors including occupational exposure to pollutants,[19] body mass index,[20] periodontitis,[21] reproductive factors,[22] smoking,[23] and dietary factors[24-26] contribute to the increased risk of developing RA. Some of these environmental risk factors may interact mechanistically with genetic risk factors to increase the risk of RA,[27] and others may have familial associations thus contributing to the familial aggregation of RA.[28;29]

Individuals with genetic and environmental risk factors for RA may progress through a phase associated with the development of systemic autoimmunity (e.g. the development of autoantibodies such as rheumatoid factor,[30;31] anti–citrullinated protein / peptide antibodies and anti-carbamylated protein antibodies[32]) before the clinical symptoms and signs of RA manifest.[9] It remains unclear whether there are changes detectable within the synovium during the phase of autoantibody positivity prior to the development of joint swelling.[33;34]

Together these data suggest that information related to genotype, environmental exposures and measures of autoimmunity and inflammation may be used to predict RA development in individuals who have not yet developed clinical disease. A potential target population for

such testing, with a view to risk stratification and intervention to modulate risk, are the first-degree relatives of individuals with RA. Indeed a number of ongoing prospective studies are recruiting the first-degree relatives of patients with RA to study disease mechanisms driving the switch to RA,[35] to develop predictive algorithms for RA, and to test interventions to reduce RA risk.[36] Whilst considerable research effort is thus focussed on the first-degree relatives of RA patients, and a qualitative study has gathered data relating to their views of preventive strategies,[37] little is known about how such individuals view issues related to their susceptibility to and risk of developing RA, and how willing they would be to be assessed and tested to have this risk quantified. The present qualitative study addresses these issues.

Methods

Ethical approval was obtained in the UK from the HumberBridge National Research Ethics Committee, in Austria from the Ethics Committee of the Medical University of Vienna and in Germany from the Ethics committee of the University of Erlangen-Nuremberg.

Procedure

Eligible participants were the first-degree relatives (offspring and siblings) of people with RA. Participants were required to be at least 18 years of age and without a diagnosis of inflammatory joint disease.

Patients with RA were approached during routine secondary care clinics in Birmingham (United Kingdom), Erlangen (Germany) and Vienna (Austria) and were given a letter to pass on to a first-degree relative of their choosing inviting them to participate in an interview about risk and predictive testing for RA. Participants were recruited between October 2014 and October 2015. It was explained to patients that it was entirely at their discretion whether to pass on the invitation letter. All research participants (i.e. the participating first-degree relatives) gave written informed consent prior to interview.

The semi-structured interviews were guided by an interview schedule which was informed by a review of the qualitative literature exploring perceptions of risk and testing in those at risk of developing a chronic disease.[38;39] The interviews aimed to assess personal perceptions of risk, therefore, one-to-one interviews were conducted. In addition, an international multi-disciplinary team of healthcare professionals, patient research partners and researchers working on the EuroTEAM project (www.team-arthritis.eu) reviewed and redrafted the interview schedule (see table 1 for sample questions from the final interview schedule).

One-to-one Interviews were conducted at local hospitals or by telephone (for those participants who had difficulty in attending the hospital for a face-to-face interview). Interviews lasted between 30 and 90 minutes and were digitally audio-recorded. In the UK, participants who wanted further information about arthritis were advised to contact Arthritis Research UK, the National Rheumatoid Arthritis Society or the local hospital's Patient Advice and Liaison Service. Participants in Austria and Germany were advised to contact the local rheumatology outpatient clinic.

The interviews were transcribed verbatim. Interviews conducted in German were translated into English following transcription. Transcripts were anonymised and analysed centrally in Birmingham, UK, by RJS.

Analysis procedure

Data collection and analysis were carried out in parallel to assess when thematic saturation of major developing themes had been achieved. The data were analysed using a thematic approach[40] facilitated by NVivo (a qualitative software programme).[41] Transcripts were subjected to line-by-line coding by RJS. Patient research partners blind coded three transcripts to develop reliable and inclusive themes informed by multiple perspectives. Discussion of the coding framework took place between researchers and patient research partners. Coding categories that lacked concordance were discussed and absorbed into the coding framework. The initial codes were then grouped into the most noteworthy and frequently occurring categories. The core themes extracted and presented here focus on

perceptions of first-degree relatives about their personal risk of RA and their views on being tested.

Results

Thirty-four first-degree relatives of patients with RA participated, 24 from the UK, 3 from Germany and 7 from Austria. Six participants were siblings of an RA patient, 26 were the adult offspring an RA patient and 2 participants had both a sibling and a parent with RA. Participants were aged between 23 and 67 years (mean 39 years) and 26 (76%) were female (see table 2 for participant characteristics). Quotations are presented in tables 3, 4, 5 and 6 and are referred to in the text using "Q" followed by the quotation code.

Understanding of family history and genetic factors as risk factors for RA

The first-degree relatives of people with RA understood that there was a hereditary component to RA (Q1), and often used the word "genetic" to describe the cause of their increased risk (Q2). First-degree relatives (from here on referred to as "relatives") recognised that they were more susceptible to developing RA than second-degree relatives (Q3). Interestingly, some felt that they were more susceptible to developing RA than other first-degree relatives because they appeared to follow other patterns of illness displayed by their relative with RA (Q4). Additional biological factors, such as being female and some environmental factors were also described as playing a role in the development of RA (Q2&5).

When considering their perceived personal susceptibility, relatives reported that there were aspects of familial risk, particularly genetic susceptibility, which they found difficult to understand. One relative felt that effectively communicating an understanding of genetic risk to the public was extremely challenging (Q6). Others felt that they needed more information about their level of risk as a relative and the specific role that genes associated with RA played in this risk (Q7).

When considering their susceptibility to RA, relatives voiced their concerns about the future, and how being at risk of developing RA was a worry for them. Those who had considered their personal susceptibility to RA, described being fearful of what they may uncover if they were to have their risk quantified. For some, the prospect of living with RA would entail great amounts of uncertainty (Q8). For many, having witnessed the impact of RA on their sibling / parent, heightened the worry they felt in relation to the possibility of developing RA themselves in the future (Q9). Interestingly, a small number of relatives had experienced joint related symptoms but had not yet sought medical advice, being fearful of the potential outcome (Q10).

Personal considerations of RA risk and communication about risk within families

Relatives discussed knowing little about RA or its risk factors, feeling that they had been "shielded" or "protected" from this knowledge by their sibling / parent (Q11). Also, relatives described how they rarely discussed RA within their family unit, and in some cases the invitation to participate in this study was the first time that the opportunity to discuss RA, and its risk had emerged (Q12). For one relative, receiving the invitation to take part in this study facilitated the first conversation he had had with his father about RA (Q13). Another described how his mother had had some concerns about him taking part in this study, because of the worry which discussing issues surrounding risk and predictive testing may cause (Q14). One relative described how her brother had been asked to take part in this study, but ignored the request; her mother had then approached her and encouraged her to participate (Q15). This relative suggested that it was her attitude towards health which set her apart from her brother.

Most relatives had not fully considered issues related to their personal susceptibility to RA prior to being approached to take part in this study (Q16). Some relatives indicated that taking part in this study had been a positive experience for them and had provided them with much needed knowledge, a chance for reflection on their risk and a greater understanding of RA and how it affected their sibling / parent (Q17). However, others described how they would prefer to avoid considering their personal risk of RA to avoid experiencing worry or anxiety about the future (Q18).

Perceptions surrounding the use of predictive tests: positive perspectives

Most relatives were in favour of the basic principle behind predictive testing - identifying those at risk and quantifying the level of risk (Q19). It was also felt that the information gained from predictive testing could be acted upon to reduce the future risk of developing RA (Q20). In particular, relatives recognised the importance of early intervention, and were aware that testing could put them "on alert" for the early symptoms of RA (Q21), or suggested that they might be able to take preventive treatment (Q22). Many relatives felt that it was important to know that they were at risk, and that information related to their actual risk would be of value to them, allowing them to "mentally" prepare for the future (Q23). Others could see the benefit of preparing for the functional limitations that may be associated with RA (Q24). A few had already undertaken predictive testing to explore their personal risk of developing RA (Q25). Some were willing to be tested for altruistic reasons such as taking part in research (Q26).

Perceptions surrounding the use of predictive tests: negative perspectives

The ability of predictive tests to quantify risk was widely discussed (Q27), with one participant questioning the specificity and sensitivity of the test (Q28). Relatives expressed a desire for tests that would, with a very high likelihood, be able to confirm or exclude the fact that they would develop RA (Q29). However, many relatives suspected that test results would give them an intermediate risk of developing RA and others highlighted concerns about "false positive" results (Q30). Some believed that predictive testing would not be able to give them answers to questions they thought were important for example how severe would their RA be were they to develop it, and when it would be most likely to begin (Q31).

Relatives were worried about the impact of testing on their family members and in particular on their sibling / parent with RA (Q32). Participants felt that by seeking information about risk and pursuing testing that they would cause their relative with RA to experience stress, worry or feelings of guilt. Participants were further worried about the stress that predictive test results may cause them. One even suggested that such stress could cause the disease to develop earlier than it otherwise would (Q33).

Relatives felt that being given risk information when they were young would be a particular burden (Q34). Instead, they felt that testing should be left until later in life, when the chance of developing a condition like RA was higher. Risk information was considered to have significant implications for future life choices and could make them "rush" though life (Q35). One relative suggested such information could bring forward major life decisions, such as having children (Q36).

Some relatives reflected upon previous negative personal experiences of having received poorly communicated test related information (Q37). For some, the approach to the delivery of risk information represented an important feature of a predictive test, and may determine whether the test would be acceptable to them. Relatives discussed how they would want to be told prior to the test what format the result would take. Some suggested that they would like to receive the results by letter, and then be given the opportunity to discuss the results with a healthcare professional (Q38). Other relatives emphasized the importance of talking to someone about the test result, especially to manage the psychological distress that may be associated with receiving a "positive" test result (Q39). Many relatives felt that there was a need for ongoing support from a healthcare professional following testing (Q40).

Discussion

This study explored the degree to which first-degree relatives of people with RA felt that they were susceptible to developing RA and their perceptions of predictive testing. Most relatives were aware that there was a genetic contribution to the risk of RA, and that they may be susceptible to developing RA; however they were unsure of the extent of the additional risk. Relatives highlighted the need for additional information about familial risk and described the need for better communication strategies in relation to imparting this information.

Generally, first-degree relatives felt that there was a need for more information and support specifically designed for the family members of people with RA. The current lack of support and information was suggested to have a number of effects, including family members not feeling able to communicate and support the person affected with RA and not feeling able to understand concepts surrounding the nature of RA and the risks associated with RA. Studies of information sharing amongst family members at risk of cancer have found that patients with the disease do not always communicate risk information in a timely or thorough fashion.[42] Forrest et al found that relatives from smaller families, and female relatives were more likely to make contact with genetic services.[43] Research has shown that genetic counselling can facilitate interfamily communication, and can help to minimize distress and increase the number of family members making contract with health services to be tested.[44;45]

An incidental finding of this research was that being invited to take part in research about risk was the first time that some relatives had fully considered their personal susceptibility to RA. In some cases this exposure was viewed positively but in other cases it caused worry and concern. It is difficult to draw conclusions about the specific impact taking part in this study had on relatives' well-being but we note that relatives did indicate that support mechanisms would be helpful to enable them to understand and cope with risk related information, especially if predictive testing were to be offered. We would suggest that

researchers accessing participants in "at risk" populations pay particular attention to the impact that an invitation to participate and participation itself may have, and offer additional support to mitigate against anxiety caused. While personal susceptibility may not have been considered, perceptions of RA severity may predict personal willingness to engage in predictive testing. It is possible that first degree relatives of people with more severe forms of RA or poorly controlled disease maybe more motivated to engage in predictive testing. This would be in line with the predictions of the health belief model.[46] A quantitative investigation to assess the effect of factors such as disease severity in people with RA, on their family members' perceptions of risk and orientation towards predictive testing is needed to test this hypothesis.

In addition, it became apparent during the course of this study that some relatives were symptomatic but had not yet sought medical help. Detailed information on the health status of the participating relatives was not gathered within this study but those who were symptomatic were advised to speak to their family physician, and were given details of resources for obtaining additional information. However, the symptomatic nature of some relatives raises important issues surrounding informing relatives about risk, and the importance of seeking help quickly should symptoms emerge. While some relatives were aware that their symptoms may be indicative of the early stages of RA, and were worried about what information would be revealed to them if they sought help, few were aware of the importance of early intervention. Were information about the benefits of early intervention in preventing joint destruction made available to them, it is possible that their attitude to help seeking may have been different.

This study has a number of limitations. Firstly, our access to first-degree relatives was via patients with RA. Some relatives described how they were chosen in preference to other relatives, who would either worry too much or not be receptive to discussing issues related to risk. The findings presented here may thus not fully reflect the range of views related to risk and testing held by first-degree relatives. This potential limitation highlights the need to fully understand the barriers that patients with RA face when discussing issues of risk with family members. A second limitation of this research was that the majority of participants were female. A criticism of many qualitative studies in the field of RA is that the male

perspective is underrepresented.[8] While the female: male ratio of RA is typically 2:1 it is essential that studies attempt to include the views of more male participants. Therefore, we acknowledge that themes related to gender and male perspectives of risk and predictive testing did not reach saturation and are not represented in our data. A final limitation is that only a small number of individuals from ethnic-minority communities were interviewed, therefore, a full understanding of the cultural barriers to predictive testing was not achieved.

Besides these limitations, this study has a number of strengths. Relatives were sampled from centres in 3 different European countries and saturation of the main themes was achieved by combining interview data from all centres; furthermore, no differences in the views expressed by relatives sampled from different European countries were detected. Gathering data from multiple countries means that interventions developed based on these data are likely to be relevant in multiple contexts. A further strength of this study was the support given by an international panel of patient research partners who advised researchers and acted as co-researchers.

Identifying individuals at risk of RA may allow targeted interventions to reduce the risk and consequence of future disease; however, our data show that relatives have concerns about predictive testing and risk information that would result from it (the key messages of this study are summarised in tabled 7). The future development of strategies to quantify and communicate risk needs to take these views into account and incorporate approaches to mitigate concerns and minimize any negative psychological impact of risk information.

Data Sharing Statement

Unpublished data is available in the form of unanalysed interview transcripts sorted in an NVIVO file from the corresponding author. Data can be obtained by emailing the corresponding author.

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Table 1: Sample interview schedule for those at risk of developing RA

- Tell me what you know about RA?

PROMPTS: What do you think the causes of RA could be? What do you think the risks factors for RA are? Tell me about how serious you think RA is? How would you know you had RA e.g what symptoms would you expect? What would be the impact of RA on your life? Do you think you would be able to control RA yourself? Do you think there are treatments available that would effectively treat RA?

- Do you ever worry about the possibility of developing RA in the future?
- What would you think if you were told that you could have a test that would tell you how likely you were to develop RA?

PROMPTS: What sort of information should this test give you? When do you think would be the right time to get this information? How would you feel about the idea of having a test that would tell you your chance of developing RA in the future? In what ways do you think it would be helpful for you to know your chances of developing RA?

- What would your concerns be if you knew what your risk of developing RA was?
- What kind of tests do you think people might be able to do to work out whether or not you might develop RA (test that are available now and tests that might become available in the future)?

Table 2: Details of first degree relatives of RA patients who participated in the interviews

Participant no.	Gender	Age	Ethnicity	Relation to RA patient	Experience of testing	Self-reported musculoskeletal symptoms	Interview country
Participant 1	Female	36	White British	Daughter	None	None	UK
Participant 2	Female	42	White British	Daughter	None	Previous septic arthritis	UK
Participant 3	Male	35	White British	Son	None	None	UK
Participant 4	Male	67	White British	Brother	None	None	UK
Participant 5	Male	31	White British	Son	Reports having had a "genetic test" for RA (performed by family physician).	None	UK
Participant 6	Female	23	White British	Daughter	None	None	UK
Participant 7	Female	30	White British	Daughter	None	Ankle pain and intermittent ankle swelling attributed by patient to a previous "ankle dislocation"	UK
Participant 8	Female	39	White British	Daughter	Rheumatoid factor	Elbow pain	UK

					previously measured		
Participant 9	Female	54	White British	Sister	None	Finger pain	UK
Participant 10	Female	35	White British	Daughter	None	"Inflamed knee" during pregnancy	UK
Participant 11	Female	44	White British	Sister AND Daughter	None	Back pain	UK
Participant 12	Female	44	White British	Sister	None	Finger pain	UK
Participant 13	Female	41	White British	Sister AND Daughter	Rheumatoid factor previously measured by family physician	Finger pain, stiffness and swelling	UK
Participant 14	Female	60	White	Daughter	Has had "blood tests" (participant unsure which)	Has a diagnosis of osteoarthritis	UK
Participant 15	Female	29	White British	Daughter	None	None	UK

Participant 16	Female	40	White British	Daughter	None	None	UK
Participant 17	Female	41	Asian (UK born)	Daughter	None	None	UK
Participant 18	Female	28	White British	Daughter	None	None	UK
Participant 19	Male	42	Chinese	Son	None	None	UK
Participant 20	Female	25	White British	Daughter	None	None	UK
Participant 21	Female	41	White British	Daughter	None	Had previous joint swelling in wrists and hands	UK
Participant 22	Female	32	White British	Sister	None	None	UK
Participant 23	Female	44	White British	Daughter	None	None	UK
Participant 24	Male	47	White British	Son	None	None	UK
Participant 25	Female	29	White German	Daughter	None	None	Germany

Participant 26	Female	37	White German	Daughter	None	None	Germany
Participant 27	Female	51	White German	Daughter	None	None	Germany
Participant 28	Female	21	White Austrian	Daughter	None	None	Austria
Participant 29	Male	33	White Austrian	Son	None	None	Austria
Participant 30	Female	65	White Austrian	Sister	None	None	Austria
Participant 31	Female	36	White Austrian	Sister	Reports having had a blood test	None	Austria
Participant 32	Male	37	White Austrian	Son	None	None	Austria
Participant 33	Male	37	White Austrian	Son	None	None	Austria
Participant 34	Female	33	White Austrian	Daughter	None	None	Austria

Table 3 Quotations related to an understanding of family history and genetic factors as risk factors for rheumatoid arthritis

Code	Quotation
Q1	*"I see that my mother has it and I'm just worried that it might be passed on to me or my sister or other members of my family." (Participant 19)*
Q2	*"In my opinion it's environmental factors or genetics." (Participant 28)*
Q3	*"So I know it's blood-related... I think if it was your cousin or your aunt there'd be a slim chance….. being direct blood-related, I would class myself as, or think of myself that I am at a higher risk than most."(Participant 6)*
Q4	*"I seem to follow my mum in absolutely everything, like my brother and sister they're quite like my dad, they never get ill, they never catch a cold. Whereas if there's a cold going around I will get it and the same with my mum… So I was a bit like 'oh, maybe I'll get it'." (Participant 18)*
Q5	*"I know that there's a genetic tendency. That it runs in families. I'm female, so I'm more at risk because I'm female… I know first degree relative increases your risk, so yeah, it does worry me." (Participant 10)*
Q6	*"Genetics really worry me because I don't know anything about them and I think when people think of genetics they think of like I don't know it's quite like a complicated thing that we're never going to understand because there's no simple way of putting it….. But like your average Joe Bloggs [average person] isn't going to know extensive information about your genes." (Participant 20)*
Q7	*"For me personally it's kind of hard facts and figures; I'm more comfortable knowing in terms of percentages. I know my dad has got rheumatoid arthritis, and if you've got a hard fact and figure to say that the chances of a close relative, son or daughter, developing rheumatoid arthritis at some point in their life then that information would be useful to me." (Participant 5)*
Q8	*"It [life] wouldn't be predictable anymore; I wouldn't know how things would be from one day to the next, or in an hour's time, when I woke up the next morning, wondering what the day would bring. I think it's pretty serious, it restricts your everyday life. And it differs – my father has pain and sometimes it's there,*

	sometimes it's not; it's unpredictable." (Participant 25)
Q9	*"I do worry about it, yeah, because I don't want to end up developing anything like that. I like to keep busy and I don't want to be restricted. It is a big worry, yeah. I don't want to go through what my mum's going through at the moment, because she's been through a lot." (Participant 13)*
Q10	*"I've got pain down my left leg [okay], but I just don't know whether it's sciatica, or whether it could be something linked to arthritis, but I'm too frightened to go and have a scan. So I probably do need it to find that. I'm just putting it off." (Participant 15)*

Table 4 Quotation related to personal considerations of rheumatoid arthritis risk and communication about risk within families

Code	Quotation
Q11	*"That's exactly what he doesn't talk to me about, he's the kind of person who leaves others out of it, deals with it by himself." (Participant 30)*
Q12	*"I am worried about that….I was quite surprised when mum said that she'd had this letter explaining about the research that you're doing." (Participant 23)*
Q13	*"He doesn't tend to talk about it. He didn't want to ask me to do this phone call, but forced himself to one day…This is probably the first time he's actually asked me to do anything and he was clearly uncomfortable." (Participant 24)*
Q14	*"I never had that information of what happens, how you're made at higher risk, I've never had that in like black and white ….which makes me think she doesn't know or maybe she's just trying to protect me like a mother does. Because I think she was quite worried about me taking part….she's quite worried about what I'd find out. (Participant 5)*
Q15	*"My mum, sort of, mentioned this to him [brother], and he was just, like, ignored the fact that she'd said anything to me. And then she came to me and said, 'I thought I'd ask your brother first but he won't,' and I said, 'I don't mind,' but he's probably different to me, just blissful ignorance, whereas I'm probably a little bit different." (Participant 2)*
Q16	*"Up until now I have never thought about it, what that would be like, whether it might happen" (Participant 28)*
Q17	*"I guess before we spoke I couldn't understand what it was exactly that was making her finger sore or swollen or anything like that. I would just be like, drink more milk." (Participant 20)*
Q18	*"You only worry too much and rack your brain, because then I have to consider that my children could get it too and then you would worry too much. It's more comfortable to avoid it." (Participant 32,)*

Table 5 Quotations related to perceptions surrounding the use of predictive tests: positive perspectives

Code	Quotation
Q19	*"I'm open to everything, well, I don't know why I shouldn't have that done, I couldn't think of a reason off the top of my head not to do it." (Participant 31)*
Q20	*"If I was offered a test, I'd be very happy to have one. I don't need to think about that. Well, it might be if it might help me combat a disease later, or at least know how to treat it. Well, if I'm at risk I think it would be helpful to know." (Participant 3)*
Q21	*"I would do that straight away, because I want to know as soon as possible, because I think the more you know the earlier, the more you can do about it." (Participant 31)*
Q22	*"I think that with kind of information, I'd be more keen to, sort of, sort out what I needed to do to try and prevent that becoming a problem. If I could take some sort of medication to…head it off before it became a big problem." (Participant 2)*
Q23	*"I think that would be a good thing. I think I'd like to know because then I may be able to prepare a bit more, like mentally as well." (Participant 20)*
Q24	*"Yes, it would. I think I would have the test just to see what the long-term forecast is, because my job's fairly labour intensive. I'd be willing to know what the future holds, just from the point of view of my job circumstances at work." (Participant 19)*
Q25	*"Actually I did get tested, but it was a long time ago." (Participant 27)*
Q26	*"I'm not averse to having them, especially, if it helps with research and stuff like that." (Participant 2)*

Table 6 Quotations related to perceptions surrounding the use of predictive tests: negative perspectives

Code	Quotation
Q27	*"Exactly, if it is only a vague presumption where they say, yes, you could perhaps out of two to five people or something, you could get it and the others wouldn't, well that is very vague. (Participant 32)*
Q28	*"That depends on the test, how specified it is and how sensitive it is, otherwise I would not have the test done." (Participant 29)*
Q29	*"Because if told me – it's only how likely, it's not a, 'You will develop it,' and it doesn't tell you when you will develop it. So I think if somebody said to me, 'There's this test out there and it'll tell you whether you might develop it,' I wouldn't want it, because you could just live your life in fear and never actually develop it. So unless it was 100% guaranteed, and somebody could say, 'You will develop it within this time frame,' I don't wanna [want to] spend the next 30 years worrying about something, when I could be enjoying those 30 years. So, no, I'd probably – it depends on the exact details of the test. (Participant 10)*
Q30	*"Or, equally, I guess, false positive. If you've got one really bad, sort of, joint that you've tested, it could, kind of, put a bit of a negative spin on it." (Participant 1)*
Q31	*"It would be nice to know when … at what point in time you were going to get ill, and how severe it was going to be … but I don't know whether a test can find that out. (Participant 25)*
Q32	*"But I wouldn't want to worry my mum by saying, can you get me a leaflet on testing. I wouldn't want my mum to worry that I was going for this test….to know that if in five years time I'll get it, I don't want her to know that because I think that would worry her more than anything." (Participant 6)*
Q33	*"On the one hand you know that you might develop the disease and it is of course stressful, because then you know, one day, when I'm about 30 – 40 years old, it will start and then my body will become weaker and I will get this disease, then it could create a lot of stress to have these negative thoughts. I don't know what the psychological effect would be on the body, whether it really might break out*

	sooner. If you don't know, so, if you say, I don't know and you live each day as it comes, meaning that it might break out at a later date." (Participant 32)
Q34	*"From personal experience, I think it would be something that when I got a bit older and certain things started going wrong with me or I started getting more illnesses I'd think I'd need to start looking to what all these problems are. At this particular moment in time, when there's generally nothing wrong with me, I just think that I don't really need to delve too much into that sort of information."(Participant 4)*
Q35	*"Yeah I kind of wouldn't want this test to tell me that I had a 50/50 chance of getting it in the next five years because that would change my entire perception on what I wanted. And I guess if someone gave me that bit of information I'd have to seriously think, well maybe I can't have that, maybe I've got to like push everything forward like get married and have kids before I start to take medication which I guess that's a lot of information I don't know about in that if I had to start taking that medication would that affect me having kids. It's like knowing when you're going to die that doesn't sit right with me either." (Participant 15)*
Q36	*"I think, if, for argument's sake, I'd gone for the test tomorrow, and the results came back and they said, 'Yeah, you're at high risk,' and in two years' time, the symptoms kicked in, you're then thinking, 'Right, okay.' We'd probably want a second child and we'd want a third, 'Let's do it now,' sort of, thing, but otherwise, I think, you know, just life would carry on" (Participant 6,)*
Q37	*"The GP [family physician] literally just sat me down, blurted some technical words out, medical terminology to me that went straight over my head and, again, didn't sink. I think, just keep simple, instead of baffling people with medical science, really, of your technical words that you use, compared to what, sort of, the general public are going to understand." (Participant 6)*
Q38	*"I'd be happy, I think, if, before the test, someone would explain the kind of outcome to expect. And then when I got the test results back, it would be okay by post, as long as there was, kind of, accompanying information. I suppose at that point you'd probably end up going to see someone anyway to talk through what tablets or whatever you could take." (Participant 1)*

Q39	*"I suppose it would be sensible to go and talk to somebody about it. (Participant 3)*
Q40	*"I think it's a good idea to talk to somebody and find out more information. I think seeing somebody on a regular basis, like every year or something, might be good if you knew that you were going to get it. Obviously, you're going to have more and more questions, aren't you? Yeah, for an update and just to see how things are going. Obviously, as time goes on, you're going to have more questions and so I think it would be good to speak to somebody." (Participant 20)*

Table 7: Key messages

1. Identifying those at risk of RA, and quantifying their risk, may help guide targeted interventions to reduce future disease burden. This qualitative study found that first-degree relatives of people with RA, who are themselves at an enhanced risk of RA, had a number of concerns in relation to predictive testing.
2. Some relatives would be unwilling to undergo predictive testing and were worried about the psychological impact of risk information. Others were more receptive and recognized that such information could facilitate the development and implementation of preventive strategies as well as encouraging prompt help-seeking and intervention at the onset of RA symptoms.
3. Developing strategies which communicate risk information effectively while reducing the psychological burden associated with this information is essential.