Received: 16 April 2023 | Revised: 12 July 2023 | Accepted: 27 July 2023

DOI: 10.1111/hae.14836

Haemophilia WFH WILEY

ORIGINAL ARTICLE

Psychological and cognitive factors involved in decision-making process of haemophilia carriers in reproductive choices

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Abstract

Introduction: Haemophilia carriers (HCs) face a multitude of psychological challenges, mainly linked to the possibility of having an affected child. Important reproductive decisions such as opting for pre-implantation genetic testing, or choosing prenatal diagnosis and then whether to continue or interrupt pregnancy in case of affected male fetus, have to be taken into consideration. Notwithstanding, the role of psychological characteristics on such decision-making process needs further investigation.

Aim: The aim of this study was to investigate whether HCs' beliefs and emotions about haemophilia and cognitive factors such as decision-making style, risk perception, coping strategies in response to stress, and need for cognitive closure might modulate HCs' reproductive decisions.

Methods: Participants were interviewed about their beliefs and emotions on haemophilia and filled an on-line standardized questionnaire on cognitive variables. Sixty HCs participated in this study.

Results: Results show that HCs with high distress for haemophilia given by negative childhood experiences for one or more family member illness and by high concern for their children's health, and with psychological traits characterized by logical (versus emotional) reasoning, active coping style and high need for certainty, tend to choose diagnostic prenatal tests over routine pregnancy analysis.

Conclusion: This study highlighted the influence of negative early-life experience with haemophilia and of several cognitive factors in HCs choice of prenatal test.

KEYWORDS
decision-making, haemophilia carriers, pre-implantation genetic testing, prenatal diagnosis, reproductive choices

1 | INTRODUCTION

Haemophilia is an X-linked bleeding disorder that results in reduced levels of coagulation factor VIII (haemophilia A) or factor IX (haemophilia B), which cause a defect in clot formation and consequent bleeding diathesis. Haemophilia A and B are inherited as an X-linked recessive trait, thus men are affected, while females are usually asymptomatic carriers of the disease. Daughters of men with

haemophilia are obligate carriers of the condition and have a 50:50 chance of passing on the condition to a son, and a 50:50 chance that a daughter will be a carrier.[1] Haemophilia carriers (HCs) and their partners have to face psychological challenges and important reproductive decisions such as opting for pre-implantation genetic testing (PGT) or for a prenatal diagnosis (PND) and, in the latter case, to choose whether perform an invasive PND (i.e. chorionic villus sampling and amniocentesis) or a non-invasive method (Non-invasive prenatal testing—NIPT or Y-PCR testing[2]). Furthermore, linked to these choices, about what to decide in case of affected male fetus.

Studies that so far investigated the factors influencing such choices have been focused mainly on the role of clinical aspects of haemophilia and of socio-demographic factors. For instance, Tedgard and colleagues[3] found that the choice to undergo PND was more common among HCs with a family history of haemophilia and with a positive attitude towards abortion following PND. A nationwide survey[4] among HCs in the Netherlands found that the choice for early prenatal diagnosis was associated with a liberal view towards termination of pregnancy, severe haemophilia in the family, absence of a religion belief, and older age.

A study about the frequency and the reasons for choosing PND in a cohort of Swedish HCs along a 30-year period,[2] found that the number of PND is stable over time (about half of pregnancies) but in later years it is chosen mostly to properly manage pregnancy and childbirth and for psychological preparation, as compared to previous years, when PND was mainly used in order to prevent the birth of a haemophilia-affected boy by termination of pregnancy[5–7]). However, as revealed by a recent review,[8] PND might still be used with the aim of terminating a pregnancy of an affected male in families with a history of severe haemophilia.[9,10]

Other studies[11–13] showed that living near a specialized medical center and having received adequate genetic counseling are factors affecting reproductive decision-making, as they increase the likelihood that the HC will decide to have children.

To our knowledge, no quantitative study has so far investigated psychological characteristics that play a role in the multifactorial decision-making process about the choice of prenatal test to be performed, and about the eventual subsequent decision in case of affected male fetus.

The aim of this study is therefore to investigate whether cognitive and emotional factors, such as decision style, risk perception, coping strategies used in response to stress, emotions and beliefs about haemophilia might modulate HCs' decisions about prenatal medical exams (namely: PGT, PND, NIPT and routine pregnancy analysis).

2 | MATERIALS AND METHODS

2.1 | Subjects

Seventy-five women carriers of severe or moderate haemophilia A and B referring to Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre in Milan Italy, who had at least one pregnancy since 2012, were contacted and asked whether they would be interested in participating in the study. An email with the informed consent and with a link to the on-line standardized questionnaire was sent to the 60 carriers who agreed to participate. A videoconference interview was scheduled for each woman.

Inclusion criteria were: being carrier of severe or moderate haemophilia; aged 18 or older; having had at least one pregnancy since 2012; being able to understand written and spoken Italian.

Exclusion criteria was having a previous psychiatric diagnosis.

This study received approval by the Ethics Committee of the IRCCS Maggiore Hospital in Milan (796_2020bis). All the phases of the study were prepared, conducted and described in accordance with the Good Clinical Practice (D.M. 15 July 1997). All participants gave their written informed consent in accordance with the declaration of Helsinki. Participants were told that they could avoid answering to any question that eventually make them feel uncomfortable, and that they could withdraw from the interview at any time.

2.2 | Study design

This research is a descriptive cross-sectional study. A questionnaire was designed and administered partly on-line and partly face-to-face through a video interview by a psychologist, given the sensitivity of some questions.

Face-to-face administered questions covered the following topics:

(1) Sociodemographic data: age, education.
(2) Haemophilia-linked variables: haemophilia type; familial versus non-familial haemophilia; physical effects of HC condition; concerns linked to the HC condition; emotions linked to haemophilia experienced in the family.
(3) Pregnancy-related variables: maternal age at last pregnancy; last pregnancy order; outcome of an eventual previous pregnancy; type of prenatal test performed in the last pregnancy; motivation for the choice; last pregnancy outcome.

The on-line standardized questionnaires investigated the following psychological traits:

(1) Decision-making style. It was assessed through the *General decision-making style* (GDMS)[14] (Italian validation[15]), a 25-item questionnaire on a five-point Likert scale that identifies five decision-making styles: Rational (refers to a logical assessment of the alternatives); Avoidant (based on attitude to postpone a decision); Dependent (that refers to the need to seek advice before taking a decision); Intuitive (that refers to the tendency to rely on intuitions, feelings and sensations); and Spontaneous (that refers to the need to quickly conclude the decision-making process).
(2) Risk-taking attitude. It is a stable and general tendency to take risks across different life-domain situations. It was assessed through the Risk Propensity Scale (RPS)[16] (Italian validation[17]) a

questionnaire composed by 7 items to be rated on a nine-point Likert scale.

(3) Coping style. It is an individual and stable tendency to deal with stressful situations. We assessed it through the *Brief Coping Orientation to Problems Experienced* (COPE-NVI)[18] (Italian validation[19]), a questionnaire composed by 25 items to be rated on a four-point Likert scale that evaluates five different copying strategies: Social support (tendency to seek advice from others); Avoidance strategy (tendency to refuse to believe the problem is real); Positive attitude (tendency to reframe the problem/stressor in positive terms); Problem-solving (tendency to take steps to eliminate the problem); Turning to religion (tendency to use faith for support).

(4) Need for cognitive closure. It is the desire for certainty. It was measured through the *Need for Cognitive Closure Scale- Short Version* (NFCS)[20] (Italian validation[21]) that includes 15 items to be rated on a 6-point rating scale. People who obtain high scores on this scale value order, dislike ambiguity, and have strong opinions. The scale also includes the following five sub-scales: Desire for predictability; Preference for order and structure; Discomfort with ambiguity; Decisiveness; and Close-mindedness.

The entire procedure required about 30 min.

2.3 | Statistical analyses

Descriptive statistics were computed for all variables: frequencies and percentages were used to summarize categorical and continuous variables as appropriate; mean (M) and standard deviation (SD) were evaluated for continuous variables, whereas frequency (n) and percentage were evaluated for categorical variables. Missing values from single items were not imputed.

A series of Chi-square tests of independence were performed to examine the relation between the type of prenatal test and psychological variables related to haemophilia and carrier condition.

A series of Analysis of Variance (ANOVA) were performed to examine the relation between the type of prenatal test and the results of psychological tests (GDMS, RPS, COPE-NVI, and NFCS).

An alpha level of .05 was used for all statistical tests.

3 | RESULTS

3.1 | Descriptive statistics

Preliminarily, we removed from the sample 6 HCs that were not aware of being haemophilia carriers at the time of their pregnancy. We thus obtained a sample of 54 carriers.

Sociodemographic data and haemophilia-linked variables are summarized in Table 1. Mean age of participants at interview was 40.8 (SD. = 4.95, range 29–49). Most HCs (81%) had a familial history of haemophilia (defined as in extended family members, not including son/s); however, those who did not ($n = 10$), were aware of their carrier status when they became pregnant (generally because in the previous pregnancy they gave birth to an affected child). Forty-three women (80%) had no symptoms related to HC condition, whereas four reported to have profuse bleeding (e.g. in case of injuries or surgeries, and menorrhagia) and seven to have menorrhagia.

The type of prenatal test performed and the motivation for the choice are reported in Table 2.

Thirty-seven HC (68%) opted to undergo prenatal invasive procedures. The motivation for this choice was mainly related to the possibility to go for pregnancy termination in case of affected fetus (57%).

Six HCs received the diagnosis of affected male fetus after PND and faced the decision to eventually interrupt pregnancy: only two of them (33%) opted for interruption. Table 3 shows last pregnancy outcome divided by the type of prenatal test.

3.2 | Inferential statistics

A series of Contingency Tables with Chi-square Tests showed that concern about one's own child health (Table 4) is significantly related with the type of prenatal test performed ($\chi^2(6, N = 54) = 19.19$, $p = .004$). Indeed, HCs who were deeply concerned about the possible consequences of their carrier status on their children health tended to choose a prenatal diagnostic test (PND or PGT) instead of routine pregnancy analysis (RPA).

Furthermore, in the subgroup of HCs with familial haemophilia, the amount of reported negative emotions related to haemophilia family history (referred to extended family members, not including sons) (Table 5) is significantly related with the type of performed prenatal test ($\chi^2(6, N = 44) = 21.89$, $p = .001$). More in detail, HCs that reported high amount of negative emotions tend to prefer a diagnostic prenatal test (PND or PGT) over RPA, whereas those who do not refer negative emotions tent to prefer RPA.

No significant associations were found with any other haemophilia or pregnancy-related variable: Haemophilia type: $\chi^2(9, N = 54) = 1.84$, $p = .994$; Family history of heamophilia: $\chi^2(3, N = 54) = 5.09$, $p = .165$; Symptoms related to HC conditions: $\chi^2(3, N = 54) = 1.65$, $p = .649$; Pregnancy order: $\chi^2(6, N = 54) = 7.68$, $p = .263$; Previous pregnancy outcome: $\chi^2(9, N = 31) = 15.746$, $p = .72$.

A series of One-way Analysis of Variance (ANOVA) were performed to examine the relation between HCs' psychological characteristics (as measured through GDMS, RPS, COPE-NVI, and NFCS) and the type of prenatal test. A statistically significant difference was found for the Rational decision-making style ($F(3,50) = 5.32$, $p = .003$): a Bonferroni post-hoc Test for multiple comparisons found that the mean value of Rational decision-making style ($p = .003$, 95% C.I. = [.942, 6.934]) was significantly higher in HCs who chose PND compared to those who chose RPA.

As concerning the COPE-NVI, a significant difference was found for the Problem-focused strategy of coping ($F(3,50) = 4.44$, $p = .010$): mean value of Problem-focused strategy was significantly higher in HCs who

TABLE 1 Sociodemographic data, clinical characteristics and pregnancy-related variables for the whole group of participants, and by type of prenatal test.

		n (%)				
		Total group (*n* = 54)	PND (*n* = 37)	RPA (*n* = 9)	PGT (*n* = 6)	NIPT (*n* = 2)
Age	29–35	9 (17%)	4 (11%)	2 (22%)	2 (33%)	1 (50%)
	36–42	21 (39%)	16 (43%)	4 (44%)	1 (17%)	–
	43–49	24 (44%)	17 (46%)	3 (33%)	3 (50%)	1 (50%)
Highest completed educational level	Secondary school	3 (6%)	2 (5%)	1 (11%)	–	–
	High school	37 (68%)	25 (68%)	7 (78%)	4 (67%)	1 (50%)
	University	14 (26%)	10 (27%)	1 (11%)	2	1
Haemophilia type	HA severe	38 (70%)	25 (68%)	7 (78%)	4 (67%)	2 (100%)
	HA moderate	9 (17%)	7 (19%)	1 (11%)	1 (17%)	–
	HB severe	6 (11%)	4 (11%)	1 (11%)	1 (17%)	–
	HB moderate	1 (2%)	1 (3%)	–	–	–
Family history of haemophilia[a]	Yes	44 (81%)	32 (86%)	5 (56%)	5 (83%)	2 (100%)
	No	10 (19%)	5 (14%)	4 (44%)	1 (17%)	–
Symptoms related to HC conditions	Yes	11 (20%)	8 (22%)	1 (11%)	2 (33%)	–
	No	43 (80%)	29 (78%)	8 (89%)	4 (67%)	2 (100%)
Maternal age at Pregnancy	27–32	14 (26%)	9 (24%)	2 (22%)	2 (33%)	1 (50%)
	33–38	23 (43%)	16 (43%)	4 (44%)	2 (33%)	1 (50%)
	39–43	17 (31%)	12 (32%)	3 (33%)	2 (33%)	–
Pregnancy order	First pregnancy	20 (37%)	16 (43%)	2 (22%)	2 (33%)	–
	Second pregnancy	29 (54%)	18 (49%)	7 (78%)	3 (50%)	1 (50%)
	Third pregnancy	5 (9%)	3 (8%)	–	1 (17%)	1 (50%)
Negative emotions linked to family history of haemophilia[b]	No negative emotions	10 (23%)	4 (13%)	4 (80%)	–	2 (100%)
	Slightly negative emotions	8 (18%)	5 (16%)	1 (20%)	2 (40%)	–
	Highly negative emotions	26 (59%)	23 (72%)	–	3 (60%)	–
Concerns for being a HC	No concern	9 (17%)	2 (5%)	5 (56%)	1 (17%)	1 (50%)
	Concern for my health	11 (20%)	6 (16%)	2 (22%)	2 (33%)	1 (50%)
	Concern for my children health	34 (63%)	29 (78%)	2 (22%)	3 (50%)	–

[a]Defined as in extended family members, not including son(s).
[b]Participants who had a family history of haemophilia were: *n* = 44 in the total group; *n* = 32 in the PND group; *n* = 5 in the RPA group; *n* = 5 in the PGT group; *n* = 2 in the NIPT group. Percentages are calculated accordingly.

TABLE 2 Type of prenatal test performed and motivation for the choice (*n* = 54).

Type of prenatal test performed	*n* (%)	Motivation for the choice	*n* (%)
PND	37 (68)	To be able to choose to have pregnancy termination in the case of affected male	21 (57)
		To be ready to better manage birth of an affected male	10 (27)
		On medical advice	6 (16)
RPA	9 (17%)	Any results would be accepted	9 (100)
		On medical advice	0
PGT[a]	6 (11%)	To be sure not to transmit the disease	6 (100)
		To avoid having a pregnancy termination in case of an affected male	0
NIPT	2 (4%)	To avoid the miscarriage risk related to PND procedures	2 (100)
		On medical advice	0

[a]Preimplantation genetic testing is available in Italy as a reproductive option since 2015, when it became legal.

TABLE 3 Pregnancy outcome by the type of prenatal test.

Pregnancy outcome	*n* (%)	Prenatal test	*n*
Female (born)	29 (53)	PND	21
		RPA	3
		PGT	3
		NIPT	2
Not haemophilic male (born)	11 (20)	PND	10
		RPA	0
		PGT	1
		NIPT	0
Haemophilic male (born)	10 (18)	PND	4
		RPA	6
		PGT	0
		NIPT	0
Haemophilic male (pregnancy termination)	2 (4)	PND	2
		RPA	0
		PGT	0
		NIPT	0
Miscarriage	3 (5)	PND	1
		RPA	0
		PGT	2
		NIPT	0

Note: The total number of pregnancy outcomes do not match the total number of pregnancies because one was a twin pregnancy.

TABLE 4 Contingency table for type of prenatal test by concern for being a HC (adjusted residuals in parentheses).

	Type of prenatal test				
	PGT	PND	RPA	NIPT	Total
No concern	1 (0)	2 (−3.3)	5 (3.4)	1 (1.3)	9
Concern for my health	2 (.8)	6 (−1.1)	2 (.4)	1 (1)	11
Concern for my children health	3 (−.7)	29 (3.5)	2 (−2.8)	0 (−1.9)	34
	6	37	9	2	54

TABLE 5 Contingency table for type of prenatal test by amount of negative emotions linked to haemophilia family history (adjusted residuals in parentheses).

	Type of prenatal test				
	PGT	PND	RPA	NIPT	Total
No negative emotions	0 (−1.3)	4 (−2.6)	4 (3.2)	2 (2.7)	10
Slightly negative emotions	2 (1.3)	5 (−.7)	1 (.1)	0 (−.7)	8
Highly negative emotions	3 (0)	23 (2.8)	0 (−2.9)	0 (−1.7)	26
Total	5	32	5	2	44

chose PND compared to those who chose RPA (Bonferroni post-hoc test: $p = .010$, 95% C.I. = [.695, 7.338]).

Furthermore, a significant difference was found for the Need for cognitive closure ($F(3,50) = 4.59$, $p = .020$): HCs who chose RPA had lower score on the need for cognitive closure (Bonferroni post-hoc test: $p = .016$, 95% C.I. = [−34.54, −2.45]) as compared to those who chose PND.

4 | DISCUSSION

In the last decade, interest for the complex decisional issues that the carrier condition poses to HCs when they face a pregnancy is growing.[8] This theme is relevant as the deriving burden might affect pregnancy: women might experience guilt and sorrow linked to the fact of being a HC,[22] and those who decide to undergo some form of diagnostic tests often experience high level of anxiety prior to receive test results, and anguish when faced with the decision whether to continue or interrupt pregnancy following a positive finding.[23]

Studies that investigated HCs experiences in the context of reproductive decision-making and prenatal diagnosis identified some decisional predictive clinical and situational factors[8,13,24–26]: the severity of the disease experienced in family, the quality of life of haemophilic family members, living near a specialized medical center, having already had a haemophilic child, having access to genetic and reproductive counseling and religious beliefs. This study investigates the role of cognitive and emotional characteristics in such process.

PND was chosen by 57% of our cohort; HCs who chose PND tend to have experienced in their youth higher levels of distress related to one or more family member illness and to experience their HC condition with concern for their children's health rather than with concern for their own health or with no concern at all, compared to those who chose RPA. This result is consistent with findings from Tedgard et al.,[3] according to which HCs with experience of the complications of haemophilia or its treatment were more in favor of PND than HCs whose haemophilic children had received modern treatment without complications.

Moreover, Punt and colleagues[27] found that HCs that had experienced severe haemophilia with extensive consequences within their families felt more anxious when preparing to have children and were more determined to avoid that their child faces the same challenges as their affected male family members. Consistently, other studies showed that main reasons for not opting for prenatal diagnosis are the belief that haemophilia is a "liveable" condition compatible with a good quality of life, and that it is not a serious enough disorder to justify pregnancy discontinuation.[4,11,28–31]

However, in our sample, not all the HCs that opted for a PND aimed at knowing the fetus condition in order to eventually terminate pregnancy of an affected male. Indeed, 10 out of the 37 HCs (27%) who performed PND claimed that they chose it in order to be ready to better manage labour and delivery of a possible affected male. This is consistent with previous findings according to which prenatal

diagnosis is also conceived as an option to prepare a management plan for delivery and puerperium.[2]

PGT was chosen by 11% of our cohort, with the motivation to be sure not to transmit the disease; this is consistent with recent data about patients' decision-making and attitudes toward PGT according to which they both aim at having a biologically related child protected from a specific disease and at avoiding a pregnancy termination.[28,32]

As concerning the decision to interrupt pregnancy, in our study 2 HCs out of the 6 that received a diagnosis of affected male decided to interrupt pregnancy. Although the low number of cases of diagnosis of affected male does not allow to draw strong conclusions, we may notice that the resulting proportion (33%) is lower than those reported by previous studies–even though such studies have shown contradictory results.[4,11,28,30,33] For instance, a much higher ratio was found by Balak et al.,[4] whose nationwide cross-sectional study among 207 Dutch carriers revealed that 82% of the 22 pregnancies positive for an affected male fetus was terminated. However, our results are consistent with studies that found that in recent years prenatal diagnosis of haemophilia is increasingly used for the purpose of properly manage pregnancy and childbirth and for psychological preparation, and less used for the purpose of pregnancy termination.[2,5,34] The reason for this change could be related to the improvement of disease treatment available nowadays.

Another relevant result of our study is that some cognitive characteristics, that are stable psychological tracts that do not vary through various life situations, have a role on the type of prenatal test chosen. Indeed, HCs who chose PND compared to those who chose RPA tend to: (1) have a rational decision-making style, characterized by an extensive search for alternatives and by a logical evaluation of all of them; (2) use a problem-focused strategy of coping, characterized by taking actions to improve the situations and by seeking for help and advice from others; (3) have higher intolerance to confusion and uncertainty.

Few studies investigated the influence of cognitive dimensions on decisions about prenatal testing. One of them, a qualitative study,[35] found that all the women that were classified as having a rational decision-making style (that the authors also call "analytical") opted for an early invasive testing, as they perceived this to be essential for resolving any uncertainty and for providing sufficient information for a decision. Furthermore, these women are also characterized by active search for information in order to examine all the possible future impacts of their choice. Furthermore, a study on the psychological variables that affect the decision to perform a specific type of NIPT[36] found that women with higher levels of concern and anxiety for the fetus showed preferences for more expanded screening panel in terms of the number of conditions that are tested. These results are consistent with the finding in our HCs cohort: a search for precise, not-probabilistic information is a way to manage uncertainty, and is characteristic of people with high intolerance to uncertainty and a high cognitive need to find a solution to ambiguous situations.

Taken together, these results outline a cognitive pattern characterized by a willingness to take actions in response to difficulties, a tendency to seek information in order to logically evaluate all the possible alternatives, and a low tolerance for uncertainties which make it preferable, when it comes to choose prenatal testing, to opt for a test that gives certainty, even if this implies accepting some risk.

The fact of knowing how some carriers' psychological characteristics interacts with their decision-making process is helpful in the counseling phase, as it may help in improving communication and in addressing emotional aspects, which ultimately facilitates decision-making. Indeed, by knowing carriers' cognitive characteristics, healthcare professionals could adapt their communication style and approach to ensure effective interactions focusing on certain key points, highlighting certain considerations over others, and addressing specific concerns. For instance, carriers who have a low need for cognitive closure, that is a low need for quick and definite answers and a great tolerance for complex and contradictory situations, will benefit from simple and concise explanations. On the other end, carriers with a low tolerance for uncertainty will require more detailed information - including all potential risks, benefits, and expected outcomes- in order to lower their anxiety.

5 | CONCLUSION

This study highlighted the influence of psychological factors in the choice of prenatal test. Results showed that HCs with high distress for haemophilia given by negative childhood experiences for one or more family member illness, by high concern for their children's health and with psychological traits characterized by rational (vs emotional) reasoning and high need for certainty prefer to perform prenatal diagnostic tests rather than routine pregnancy analysis.

Such results and future researches may help healthcare providers to support HCs decisional processes in the prenatal care domain, with the aim of increase awareness and lighten the emotional burden of decision-making.

AUTHOR CONTRIBUTIONS

I.C., M.M., G.P. and F.P. designed the study. I.C. carried out the survey. I.C., M.M. and I.G. processed the experimental data. I.C. performed the analysis and drafted the manuscript. All authors contributed to the final version of the manuscript. F.P. supervised the project.

ACKNOWLEDGEMENTS

The study was partially supported by the Italian Ministry of Health—Bando Ricerca Corrente 2022. The Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico is member of the European Reference Network (ERN) EuroBloodNet.

CONFLICT OF INTEREST STATEMENT

I.C., M.M., I.G. and G.P. have no competing interests. FP: speaker fees for educational programmes/symposia organized by Spark and Takeda. Advisory boards/consultant for Sanofi, Sobi, Roche, Biomarin, CSL Behring.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy concerns related to the presence of sensitive data.

ETHICS STATEMENT

This research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements. All participants gave written informed consent to participate in the study.

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How to cite this article: Cutica I, Mortarino M, Garagiola I, Pravettoni G, Peyvandi F. Psychological and cognitive factors involved in decision-making process of haemophilia carriers in reproductive choices. *Haemophilia*. 2023;1-7. https://doi.org/10.1111/hae.14836