Swedish large-scale schizophrenia study: Why do patients and healthy controls participate?

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Abstract

Insights into determination of study participation are useful for researchers, clinicians and for ethical considerations. Few large-scale genomic studies have involved motives for enrollment, in schizophrenia patients and unaffected controls. In a case-control study with participants recruited nation-wide in Sweden between 2005 and 2010, semi-structured interviews on motives and attitudes towards future studies were explored in 2767 schizophrenia cases and 4466 controls. In qualitative and quantitative analyses, we identified altruism as a major determinant in 84% of the cases and in 97% of the controls. Among pre-defined subcategories of altruism, cases with schizophrenia were more often referring to science for example, ‘I want to help science move forward’ or ‘I want better medications for future generations’ in relation to unaffected controls that were more often referring to common humanity such as ‘It is my duty and responsibility to help’. In schizophrenia, motives related to personal benefit and social influence were reported by 9% and 5%. We conclude that individuals with schizophrenia frequently report altruistic motives for study participation, almost to the same extent as unaffected controls. In contrast to unfortunate stereotypes, people with schizophrenia wish others to benefit from their experiences with severe mental illness and should not be refrained from participating in genomic research.

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1. Background

Schizophrenia is a severe and debilitating disorder that often has major consequences for the individual’s health status (Owen et al., 2016). Advances in genomic research have exposed the importance of genetic factors in schizophrenia (Sullivan et al., 2012) and many anticipate that this research will eventually prove to be important for the development of diagnostic methods and novel treatment strategies. Voluntary research participation is essential for achieving scientific progress, but during the past decades, participation rates have declined and for case-control studies in particular (Galea and Tracy, 2007; Morton et al., 2006). For the generalizability of research findings, factors that may affect study participation, for example demographic attributes such as gender, age, socioeconomic factors, and severity of health status are important to consider (Cooley et al., 2003; Hunninghake et al., 1987; Walter and Davis, 2016). Those factors are likely to be affected by individuals’ attitudes and motives towards research participation and therefore insights into this area are important.

Schizophrenia typically presents with severe psychiatric symptoms and cognitive impairments, which may themselves affect the willingness and ability to participate in research. Previous studies suggested that individuals with schizophrenia have a worse ability to make informed decisions (Dunn, 2006), are more easily convinced to take part in research (Carpenter et al., 2000; Chong et al., 2009; Roberts, 2002), and are more prone to misunderstandings of the research goals (e.g. the therapeutic misconception) (Appelbaum et al., 1987). Nevertheless, other studies found that participants with mental disorders including schizophrenia express similar views as healthy controls regarding ethical aspects of research (Roberts and Kim, 2014).

Genomic studies usually have a low risk for physical harm as compared to studies including medical or pharmacological interventions. On the other hand, genomic research can be perceived as invasive and does not currently lead to any benefits for the participant (e.g., identification of a cause for schizophrenia), and there is an ongoing debate on how to return genomic results to individuals (Lázaro-Muñoz et al., 2018). Considering the lack of benefits, the major reason for participation in genomic studies would be altruistic motives such as a wish to contribute to research with potential benefits for future populations.
generations (Hallowell et al., 2010). Previous studies have demonstrated that altruism is an important motive for study enrollment in clinical trials (Godskesen et al., 2015; McCann et al., 2010; Rosenbaum et al., 2005) and for enrollment in genomic studies (Goodman et al., 2018). Research also demonstrated that in patients with schizophrenia, altruism was a highly prominent motive for participating in a hypothetical clinical trial (Morán-Sánchez et al., 2018; Zullino et al., 2003).

Further insights into what motivates individuals to participate in schizophrenia research may facilitate the planning and implementation phases of a study as well as for ethical considerations. Until now, few studies have focused on attitudes and motives to study participation in large-scale genomic studies and particularly involving vulnerable groups such as individuals with schizophrenia. In the present report, we aim to study differences between participants diagnosed with schizophrenia and unaffected controls regarding motives for participating in a genomic study and the willingness for future study participation. We hypothesized that 1) altruism would be the major motive in both groups, 2) individuals affected from schizophrenia would be over-represented among participants referring to de-stigmatization, social influence, or the prospect of getting a reward as motives for enrolling, and 3) individuals with schizophrenia would be less inclined to future study participation.

2. Methods

2.1. Participants

The participants were recruited to the Swedish Schizophrenia Study (S3), a population-based case-control study, with the goal to explore the genetic risk for schizophrenia (Ripke et al., 2013). Individuals with two or more hospitalizations for schizophrenia or schizoaffective disorder according to the International Statistical Classification of Diseases (ICD-8: 295, ICD-9: 295, ICD-10: F20) were identified through the National Patient Register (NPR, Socialstyrelsen). Those who met the inclusion criteria (aged from 18 years or above, residing in Sweden, and born in any of the Nordic countries of Sweden, Finland, Norway or Denmark) were invited to participate. Unaffected controls residing in Sweden, 18 years or older, and born in any of the Nordic countries, were randomly selected by Statistics Sweden and group matched by age to the schizophrenia population. Unaffected controls were not allowed to have any previous hospitalization for schizophrenia (ICD-8: 295, ICD-9: 295, ICD-10: F20) or bipolar disorder (ICD-8: 296, ICD-9: 296, ICD-10: F30 or F31). Initially, 18,487 unaffected controls and 18,190 schizophrenia cases identified through the National Patient Register were invited to participate. In total 5273 individuals with schizophrenia and 6483 not affected controls accepted to participate and were enrolled between the years 2005 and 2010, which gave a highly conservative participation rate of 29% and 35% respectively (Fig. 1). The participation rate was lower than rates presented in a review by Morton and co-workers (Morton et al., 2006). Participants received a small gift (value $20) for their participation. All procedures were reviewed and approved in advance by the Regional Ethical Review Board in Stockholm, Sweden. All subjects provided written informed consent for a broad set of genetic and phenotypic analyses that encompass all analyses reported in this paper.

2.2. Interview procedure

All participants completed a semi-structured interview and donated a blood-sample for genetic analysis. Participants with schizophrenia were contacted by a research nurse and were interviewed during a personal meeting, while unaffected controls were interviewed over telephone. During the interview, demographic information was obtained as well as information on life-style, somatic conditions, and two final questions regarding motives for enrollment in S3: 1) What made you decide to enroll in the study?; and 2) Would you agree to participate in another study in the future? The first question was open-ended and participants were asked to answer in their own words (typically one or two sentences). The second question presented the alternatives “yes”, “no”, “do not know” and “do not want to answer”.

2.3. Categorization of answers to the open-ended question

To perform a quantitative analysis of the responses to the open-ended question the two assessors (YED and HW, master students in psychology) categorized responses according to themes that were identified, that was independently validated (by VJ, Medical Doctor and specialist in clinical psychiatry). In this procedure, the raters were blinded from all information about the participants including case-control status. First, after evaluating a random sample of 300 answers the following recurrent themes were identified in the responses: “Altruism”, “Personal benefit”, “Reward”, “De-stigmatization”, and “Social influence” as well as “Non-informative answer” and “Missing answer” (Table 1). A separate category of individuals was identified, who stated that they choose to participate because they were health care professionals, but this category was collapsed with the category of “Altruism”. Second, we categorized all participant responses. If there were two or more motives stated that belonged to different categories the first one was chosen, and if the first answer was non-informative the first stated informative answer was chosen. For examples of responses and categorization into themes, see Table 1.

2.4. Sub-categories of altruism

Responses classified as altruism was further explored and divided into three different subcategories of altruism according to Carrera et al. (2018). The categories were: “Common humanity” (e.g. to make a contribution, for the future, to help people with diseases, “I have the disease, or diseases run in the family”,”Connection to science” (e.g. to contribute to science, contribute to new medications, contribute to increased knowledge/understanding, solve problems within the medical area), and “Connection to community partner organization” (e.g. “I know about Karolinska Institutet”, “I trust principal investigator’s name”).

2.5. Statistical analyses

Descriptive statistics were presented as frequencies and percentages for categorical data. For normally distributed continuous data, means and standard deviations were presented and for not normally distributed data, medians and interquartile ranges were presented. Group differences for descriptive data were calculated using Student’s t-test for continuous data or Pearson χ2-tests for categorical data.

Pearson χ2-test was used to analyze for statistically significant differences between unaffected controls and schizophrenia regarding expected and observed frequencies of motives towards study participation and for the subcategories of altruistic motives. To analyze for sex differences regarding motives towards study participation Pearson χ2-test was used separately in unaffected controls and schizophrenia. For significance tests, an alpha level of 0.05 was used. A multinomial logistic regression model was fitted to analyze for differences between unaffected controls and schizophrenia regarding future study participation. An affirmative response of “Yes” was used as reference and the odds for responding “No” or “I don’t know” were analyzed. Adjustments were made for sex and age at participation. Two-sided p-values of <0.05 corresponding to two-sided 95% confidence intervals not covering the value one were considered as statistically significant. Analyses were performed in the statistical software SAS 9.4.
3. Results

3.1. Characteristics of the sample

In total, 5273 survey responses from participants with schizophrenia and 6483 responses from unaffected controls were processed (Fig. 1). There were non-informative responses from 1772 (33.6%) of the individuals with schizophrenia and from 1630 (25.1%) of the controls. Responses were missing in 734 (13.9%) of the individuals with schizophrenia and 387 (6.0%) of the controls. For analysis, we ended up with responses from 4466 controls and 2767 cases with schizophrenia (Fig. 1). There was a statistically significant higher proportion of males and a slightly lower mean age in the schizophrenia group (Table 2).

3.2. Motives for study participation

Altruism was the most prominent motive for study participation in unaffected controls (96.9%) as well as in schizophrenia (83.7%, Table 3). The proportion of individuals referring to altruistic motives was lower in schizophrenia, but motives relating to personal benefit (9.4%) and social influence (4.8%) were more common in schizophrenia than in the controls (Table 3). Motives related to reducing stigma and receiving a reward were unusual overall, but more common in schizophrenia and only 76 individuals, in total representing 1% of the sample, referred to any of these motives. The differences in the distribution of motives between unaffected controls and schizophrenia were statistically significant ($\chi^2 = 424.2$, $p < 0.0001$, Table 3).

3.3. Sub-categories of altruism in schizophrenia and unaffected controls

From the responses that referred to altruism in schizophrenia and unaffected controls, we identified motives related to three subcategories: Connection to common humanity, Connection to Science, and Connection to Community Organizations (Carrera et al., 2018). Altruistic motives referring to Connection to common humanity was the most common motive overall and was more common in controls (65.4%) than in schizophrenia (58.1%, Table 4). Altruistic motives referring to
Examples from the categorization procedure into themes of the open-end question: What made you decide to enroll in the study?

| Category of motives | Examples                                                                 |
|---------------------|--------------------------------------------------------------------------|
| Altruism            | A wish to help others, to support research or to pay back out of gratitude towards health care. Phrases included “duty”, “solidarity”, “good deed”, “to be of help”, “to be useful”, and “to make a contribution”. |
| Health care         | Included into the “Altruism” category. Respondents referring to their occupational status in health care. |
| Personal benefit    | Hope of personally getting better, get a better insight or receive a better medication. Getting the chance to prove oneself to be incorrectly diagnosed. Curiosity of one’s own genetic makeup. Hope of getting help for relatives. |
| Reward              | The prospect of getting the reward offered to all participants.          |
| De-stigmatization   | Wishes to “break taboos”, “fight prejudice” and “contribute to a greater understanding” of psychiatric disorders. |
| Social influence    | Motivations related to being persuaded to participate or encouraged to enroll. Wordings like “NN thought that I should take part”, “I was influenced” or “I couldn’t decline”. |
| Non-informative     | Irrelevant and non-informative answers like “I had no reason not to”, “why not?”, “I don’t know” or “I received a letter”. |
| No answer           | No answer provided because the subject was not asked, did not want to reply or because the interview was discontinued. |

Connection to Science were more common in schizophrenia (41.2%) as compared to unaffected controls (34.2%). A smaller number of the participants referred to motives related to Connection to Community Organizations, unaffected controls (0.50%) and schizophrenia (0.65%). The differences in the distribution of sub-categories between schizophrenia and unaffected controls were statistically significant ($\chi^2 = 32.5, p < 0.0001$).

3.4. Attitudes towards future study participation

In individuals with schizophrenia, 82.7% answered affirmative to the question whether they would consider participating in future research projects as did 93.6% of the unaffected controls (Table 5). Participants with schizophrenia were more likely to answer “No” (OR: 7.9, 95% CI: 5.3–11.5, $p < 0.0001$) or “I don’t know” (OR: 2.9, 95% CI: 2.4–3.4, $p < 0.0001$) relating to future study participation (Table 5) as compared to unaffected controls, and group differences remained after adjusting for sex and age.

3.5. Sex differences in motives for study participation

Minor sex-differences were found regarding motives for study participation in the participants with schizophrenia ($\chi^2 = 12.4, p < 0.015$), but not among the unaffected controls ($\chi^2 = 7.3, p < 0.12$).

Table 2

|            | Unaffected controls | Schizophrenia |
|------------|---------------------|---------------|
| Sex        | Frequency (%)        | Frequency (%) |
| Male       | 2258 (50.6)          | 1583 (57.2)   |
| Female     | 2208 (49.4)          | 1184 (42.8)   |
| Mean age at sampling | 560 (11.1)       | 523 (11.5)    |
| Number hospital admissions for schizophrenia | 26 (21–32)        | 12 (6–22)     |
| Number hospital days for schizophrenia | 380 (169–868)     |               |

$^a$ Pearson $\chi^2$-test ($\chi^2 = 30.3, p < 0.0001$).

$^b$ Values are presented as mean (standard deviation).

$^c$ Student’s $t$-test ($t = 3393.9, p < 0.0001$).

$^d$ Values are presented as median (interquartile ranges).

Table 3

MOTIVES FOR STUDY PARTICIPATION.

| Motives:                      | Unaffected controls | Schizophrenia | Statistic$^a$ |
|-------------------------------|---------------------|---------------|--------------|
|                               | Frequency (%)        | Frequency (%) | $\chi^2$     | $p$-Value    |
| Altruism                      | 4226 (96.8)         | 2315 (83.7)   | 424.2        | <0.0001     |
| Personal benefit              | 45 (1.0)            | 260 (9.4)     |              |             |
| Social influence              | 79 (1.8)            | 132 (4.8)     |              |             |
| De-stigmatization             | 7 (0.16)            | 34 (1.2)      |              |             |
| Reward                        | 9 (0.20)            | 26 (0.94)     |              |             |

There were statistically significant differences in the distribution of motives for study participation between unaffected controls ($n = 4466$) and schizophrenia ($n = 2767$).

$^a$ Pearson $\chi^2$-test.

3.6. Participants who responded non-informatively regarding motives for study participation

In 1630 of the unaffected individuals (representing 25.1% of the total number of unaffected individuals) and in 1772 of the participants with schizophrenia (representing 33.6% of the total number of participants with schizophrenia), the motive for participating was classified as non-informative (Supplement Table 3). Among individuals with schizophrenia who answered non-informatively, a larger proportion were males and a lower proportion responded affirmatively to the question whether they would participate in future research projects as compared to unaffected individuals (Supplement Table 3).

4. Discussion

In this case-control study on the genetic risk for schizophrenia, we explored the motives for study participation and the willingness for future participation. In the qualitative analysis of open-ended answers, altruism emerged as the single major motive for participation overall, in unaffected individuals (97%) as well as in individuals with schizophrenia (84%). Further, we found that about two-thirds of the responses related to altruism were due to common humanity, while about one-third of the altruistic responses referred to a willingness to contribute to science. Although altruism was the dominating motive overall, in schizophrenia, motives related to personal benefit (9%) and social influence (5%) were more common. Contrary to our initial hypothesis, de-
stigmatization or the opportunity to receive a reward were rarely reported motives. The willingness for future research participation was overall high in the unaffected controls (97%) and slightly lower in schizophrenia (84%).

Altruism as a motive for study participation in genomic studies is consistent with previous survey research on general population-based samples (Cassileth et al., 1982; Kettis-Lindblad et al., 2006). In one genomic study on individuals at cardiovascular risk, 44% of the participants reported altruism as one of several motives (Facio et al., 2011). Similarly, in psychiatric populations, altruism emerged as a motive for participating in clinical studies (Chong et al., 2009; Morán-Sánchez et al., 2018; Zullino et al., 2003), and for research participation in general (Roberts, 2005). Zullino et al. reported that 87% of patients with a psychiatric diagnosis expressed altruistic motives for participating in a hypothetical clinical study (Zullino et al., 2003), and 62% of the participants reported altruistic motives for participating in a randomized clinical trial (Chong et al., 2009), although personal benefit was also as important as a motive. Interestingly, we found that participants with schizophrenia, who reported altruistic motives, were more likely in relation to unaffected individuals, to refer to science as a motivator for study participation e.g., “I want to help science move forward” or “I want better medications for future generations”. Unaffected individuals were instead more often referring to connection to common humanity that included motivations such as “it is my duty to help” but also health related motivations such as “to help people with diseases”.

Around 9% of the participants with schizophrenia referred to motives related to personal benefit e.g., “I want to know if I can get healthy”, “I want to get a better insight”, “I want to learn something new about my disease” or motives related to help their own children, family members or other closely-related people. In previous research, personal benefit emerge as a motive in genomic studies as a wish to receive personalized health related information (Gollust et al., 2012; Sanderson et al., 2016), e.g. information on prognosis through their personal genetic risk (Facio et al., 2011), rather that promoting scientific regulations.

As expected, motives of social influence were primarily reported by participants with schizophrenia, although overall, those responses constituted a relatively small fraction. Typically, for those responses were that the participant described how he or she was persuaded into participating, by a family member or by someone within the health care system, for example a psychotherapist or a nurse. Research participation is based on the ability to understand the informed consent, and there have been warnings that patients with schizophrenia could be more easily persuaded to participate in research trials (Roberts, 2002) or attracted by financial compensation (Marson, 2005). In addition, the decision making capacity is reduced in schizophrenia in relation to other patient groups, but an enhanced informed consent may overcome some of those differences (Hostiuc et al., 2018). Therefore, from an ethical perspective, it is important that studies involving vulnerable research subjects, make sure that those individuals are capable of making informed decisions about enrollment (Bracken-Roche et al., 2017). The relatively low proportion of responses related to social influence may however reflect that the structure of the recruitment and process of informed consent in the current study was fair and according to ethical regulations.

The motives of de-stigmatization and receiving a reward were unusual, but were more commonly referred to by the participants with schizophrenia. Individuals with psychiatric disorders are more likely to have a precarious financial situation, and research show that this group is more attracted by financial compensation (Marson, 2005). However, the participants received a relatively small gift, which may explain why the “reward” motive was rare. The low occurrence of motives related to reducing stigma may be explained by the objectives of the study that were oriented towards genomics.

In line with previous research, the majority of the participants were positive towards future study participation (Walter and Davis, 2016). However, the participants with schizophrenia were more likely to express unwillingness or hesitation and this again highlights the importance of taking into account ethical aspects when including vulnerable groups in research (Bracken-Roche et al., 2017). No overall sex differences were found in the unaffected individuals, while in schizophrenia, females were more prone to report motives related to reducing stigma or motives related to personal benefit. Despite small differences, this may be of interest to explore in future research.

### 5. Strengths and limitations

The strength of the current study is the large number of both patients and unaffected controls, obtained by means of a population-based sample, representative for the general population. Important limitations of this study include the low overall participation rate as compared to previous studies. For example Morton and co-workers found a median participation rate of 74–84% in population based case-control studies (Morton et al., 2006). However, the authors pointed out that the participation rate has declined from 1970 and onwards, which may partly explain the low participation rates in the present study. However, limited by ethical regulations preventing us to identify individuals who had refused participation or were non-responders, we were not able to further examine reasons for non-participation. Particularly, for individuals with schizophrenia, barriers related to the disease itself may have influenced the decision not to participate (Woodall et al., 2011). The differences in the sampling procedure in which controls were interviewed over the phone and patients with schizophrenia in a personal meeting may have introduced a systematic bias to

## Table 5

| Willing to participate in future studies | Unaffected controls | Schizophrenia | Model 1* | Model2 |
|-----------------------------------------|---------------------|--------------|----------|--------|
| Frequency (%)                           | Frequency (%)       | Odds-ratio (95% confidence interval) | Odds-ratio (95% confidence interval) |
| Yes                                     | 4129 (93.6)         | 2230 (82.7)  | 6.8 (4.6–10.0) | 7.9 (5.3–11.7) |
| No                                      | 33 (0.75)           | 121 (4.5)    | 2.6 (2.2–3.0)  | 2.9 (2.4–3.4)  |
| Don’t know                              | 250 (5.7)           | 346 (12.8)   | Ref.       | Ref.   |

The analysis is based on 4412 unaffected and 2697 individuals with schizophrenia. Not included missing responses in unaffected individuals (N = 54) and schizophrenia (N = 70). Multinomial logistic regression was used for analysis with an affirmative answer (Yes) as reference. An odds-ratio greater than one indicate that individuals with schizophrenia are more likely to answer, “No” or “Don’t know” to the question of willingness to participate.

* Adjusted for sex and age at participation.

p-Value <0.0001.
our results. A personal meeting could potentially make the participant more willing to research, thus affecting the responses to the study questions. For example, the number of individuals with schizophrenia who responded affirmatively to future study participation could potentially have been overestimated in relation to the unaffected participants. Finally, although altruism was the single most prominent motive in the study sample, a large proportion of the answers were non-informative, which may possibly be a limitation to our conclusion.

6. Implications

Insights into what motivates individuals to participate in genomic research and particularly vulnerable research subjects may facilitate future collaborations between scientists and clinicians in scientific research involving patients. This study shows that it is in practice possible to gather information on motives from a large number of study participants. Future research should focus on how to facilitate participation in genomic research and particularly for individuals with severe psychiatric conditions. For example by exploring motives for non-participation, e.g. mistrust towards scientists, fear of scientific misconduct, or misuse of personal and genomic data.

7. Conclusions

Individuals with schizophrenia reported altruistic motives almost to the same extent as the unaffected population. In addition, there was an overall positive attitude to future research participation, also in the participants with schizophrenia. In schizophrenia motives related to social influence were more frequently reported, which may reflect the vulnerability of this patient category. In contrast to unfortunate stereotypes, we conclude that people with schizophrenia wish to have others benefit from their experiences with severe mental illness. In future genomic research, individuals with severe psychiatric disorders should not be refrained from participating in research.

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CRediT authorship contribution statement

Patrick F Sullivan was responsible for the data collection and the overall study design. Viktorija Johansson came up with the idea, and Ylva Eriksson Dufva, Henritta Westman, and Viktorija Johansson performed qualitative and quantitative analyses of the data. Viktorija Johansson, Ylva Eriksson Dufva, Henritta Westman, Ulrik Khilbom, and Patrick F Sullivan contributed to the writing of the manuscript. All authors have read and approved the manuscript.

Declaration of competing interest

None of the authors reports any conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2021.01.007.

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