Public Knowledge about Monogenic Diseases and Attitudes Toward Expanded Carrier Screening in China

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Abstract

Monogenic diseases affect about 10 in 1000 live births globally and account for 20% of infant mortality and 18% of pediatric hospitalizations. Many monogenic disorders could be prevented by offering expanded carrier screening (ECS) to the general population. China is a densely populated country with 56 ethnic groups and a high incidence of congenital disabilities. Genetic variation in different ethnic groups in China has been reported. At present, the implementation of ECS in China is sporadic. There is limited data on the knowledge and acceptance of ECS in China. The purpose of our study was to assess public knowledge about monogenic diseases and attitudes toward ECS in China. Our study classified the population into the medical staff and general population to evaluate the knowledge gap and provide a reference for ECS's education programs. Using the Questionnaire Star platform, we provided the QR code of the questionnaire survey online for the general public nationwide. The respondents filled in the questionnaires through the mobile phone after scanning the WeChat QR code. We found that although the public had little knowledge about monogenic disease and ECS, most of them showed a positive attitude. Our cross-analysis showed that medical staff had more knowledge compared to the general population. Pre-test education for ECS can be carried out by medical staff who are not qualified for genetic counseling. ECS training for medical staff, especially obstetrician-gynecologist and nurse in the department of Obstetrics and Gynecology, can reduce the workload of genetic counseling.

Introduction

Although rare, monogenic disorders affect about 10 in 1000 live births globally('World Health Organization. Monogenic diseases. ') and account for 20% of infant mortality and 18% of pediatric hospitalizations(Kingsmore 2012).

Many monogenic disorders could be prevented by offering expanded carrier screening (ECS) to the general population(Kingsmore 2012). New advanced and decreasing costs of genetic analysis technologies such as next-generation sequencing (NGS) enable carrier screening in a wide range of disorders(Henneman et al. 2016; Bell et al. 2011; Hogan et al. 2018). In one of the earliest studies, Bell et al. utilized NGS to screen for pathogenic mutations in 437 genes associated with severe genetic disorders. They reported that each patient’s genome contained 2.8 recessive mutations on average(Bell et al. 2011).

China is a densely populated country with 56 ethnic groups and has a high incidence of congenital disabilities(Dai et al. 2011; Zhang et al. 2010; 'National Bureau of Statistic of the People’s Republic of China.The Sixth National Population Census, Vol 2010'). The prevalence of α-thalassemia and β-thalassemia carriers is 7.8% and 2.2%, respectively, in the Chinese population(Lai et al. 2017). Genetic variation in different ethnic groups in China has been reported(Yao et al. 2014; He et al. 2017; Xiong et al. 2010). Estimating the prevalence of carrier couples of autosomal recessive disorders in the Chinese population with ECS is difficult, as this depends on the number of diseases included in different ECS panels(Cheng et al. 2020). A pilot study of ECS for 11 autosomal recessive diseases in Southern China

showed that around 27.49% of individuals were carriers for at least 1 of 11 selected conditions. The most common one was α-thalassemia(Zhao et al. 2019). Even when thalassemia is removed from their analysis, 10.02% of the individuals were positive for at least one selected disorder. This study revealed a wide range of carrier frequencies among the various ethnic groups in Southern China, highlighting the potential value of ECS(Zhao et al. 2019).

In 2016, the European Society of Human Genetics developed and published the recommendations for the responsible implementation of ECS(Henneman et al. 2016). In 2017, the American College of Obstetricians and Gynecologists (ACOG) suggested that ethnic-specific, pan-ethnic ECS are acceptable strategies for pre-pregnancy and prenatal carrier screening('Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine' 2017). However, ECS is not a common practice in most countries(Ekstrand Ragnar et al. 2016; Borry et al. 2011). Public perception of ECS is diversified(De Wert, Dondorp, and Knoppers 2012; Facio et al. 2013). There is no policy regarding NGS-based diagnostic screening of ECS in China now. There is currently no consensus towards universal or targeted NGS-based screening of ECS in China.

At present, the implementation of ECS in China is sporadic. There is limited data on the knowledge and acceptance of ECS in China. The purpose of our study was to assess public knowledge about monogenic diseases and attitudes toward ECS in China. Our study classified the population into the medical staff and the general population to evaluate the knowledge gap between them and provide a reference for ECS's education programs. The medical staff we invited for this study included obstetrician-gynecologists and nurses in the department of Obstetrics and Gynecology.

Methods

Study setting

It was a survey-based cross-sectional study in Chinese. Using the Questionnaire Star platform(https://www.wjx.cn/), we provided the QR code of the questionnaire survey online for the general public population nationwide. Meanwhile, we randomly invited several medical staff working in hospitals to participate in the survey, including obstetrician-gynecologists and nurses in the department of Obstetrics and Gynecology. Except for obstetrician-gynecologists and nurses in the department of Obstetrics and Gynecology, other medical staff were not included in our study. To know whether there is a gap in knowledge about monogenic diseases and ECS between medical staff and general population, we specifically asked participants to choose whether they were medical staff in one of the questionnaire items. The respondents filled in the questionnaires through the mobile phone after scanning the WeChat (a social media application software developed by Tencent) QR code. The online questionnaire assessed knowledge about monogenic diseases and attitudes toward ECS.

Questionnaire development

A draft questionnaire was designed based on a review of the published literature. It was reviewed for content validity by two consultants outside the study team and edited for clarity after pilot-testing on ten couples and ten medical staff. The final version of the survey consisted of 24 single-choice questions (Additional File 1). It collected demographic information and had two sections to explore the participant's knowledge on monogenic diseases and attitudes toward ECS. We used seven items to assess the knowledge of the respondents and nine items to assess their attitudes.

The questionnaire started with a cover page describing the aims of our study, consent, and confidentiality. After reading the cover page, people could choose to enter the questionnaire or opt out. It's voluntary. Participants were assigned a unique identification (ID) number that was used on all data collection and statistical analyses when submitting the questionnaire. Each mobile device was allowed to access the online questionnaire once to avoid duplicate responses.

Based on a confidence level of 95%, a confidence interval of 3%, and a population size of 14650 000 (the number of births in China in 2019), and using a power calculation tool (www.surveysystem.com/sscalc.htm), we calculated that we would need a sample size of 1067.

Recruitment of participants

The WeChat online survey allowed investigator access to large samples of demographically diverse respondents from across the whole country. We put the generated QR code on an electronic poster, which clearly describes our survey's content, the time needed to complete the questionnaire, etc. We also made it clear on the poster that the survey was anonymous, confidential and voluntary, and thanked all those who participated.

Survey respondents were recruited in one of two ways.

1. We posted electronic posters with QR codes on our WeChat Moments. People saw this electronic poster when they browsed WeChat Moments.
2. We printed out the electronic poster with the QR code, posted the poster in the waiting area of the hospital outpatient clinics (both Zhejiang Xiaoshan Hospital and The Third Affiliated Hospital of Guangzhou Medical University), and invited people to scan the code to participate in the questionnaire survey.

A total of 1947 questionnaires were collected from November 11,2020 to February 10, 2021: 1022 were recruited through the hospital outpatient clinics (1022/1400, a 73% response rate; this relates to those who agreed or declined to complete the survey when approached); 925 were recruited through WeChat Moments (we are unable to calculate a response rate, as we cannot identify how many people viewed the survey invitation). The 1,947 respondents were from different provinces in China. The population distribution map can be generated automatically by Questionnaire Star software (Additional File 2). Two hundred and eighty-four questionnaires were excluded from further analysis because they were other

medical staff rather than obstetrician-gynecologists or nurses in the department of Obstetrics and Gynecology. The remaining 1663 cases were incorporated into the final analysis.

Data analysis

Statistical analysis was performed using IBM SPSS Statistics 26 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were computed for all items. Categorical data were reported as frequencies and percentages. The differences were assessed using the chi-square test, with $P < 0.05$ considered significant.

Ethical considerations

This survey was approved by the Ethics committee of the Third Affiliated Hospital of Guangzhou Medical University and Zhejiang Xiaoshan Hospital. Before filling in the questionnaire, online informed consent was obtained from all participants on the cover page. It's voluntary. All responses were recorded anonymously and confidentially.

Results

Demographic data

Table 1 summarizes the demographics of the respondents. In the whole cohort, 89.6% (n = 1490) was female and 10.4% (n = 173) was male. Marital status reported by the respondents was as follows: 90 (5.4%) single, 1550 (93.2%) married, 22 (1.3%) divorced, and 1 (0.1%) widowed. Age was divided into four groups: 18-25, 26–34, 35–44, and 45-50. The level of education reported by respondents included 14 (0.8%) no education or primary education, 193 (11.6%) lower secondary education, 135 (8.1%) technical secondary education, 120 (7.2%) upper secondary education, 389 (23.4%) college education, 646 (38.8%) undergraduate education, and 166 (10.0%) graduate education. In the respondents, 672 (40.4%) did not have children, and the remaining 991 (59.6%) had one or more living children. In the respondents, 149 (9.0%) had a family history of a genetic condition, and the remaining 1514 (91.0%) did not. In the individuals surveyed, 971 (58.4%) were currently pregnant (partner or self), 105 (6.3%) were considering a near-future pregnancy, and 587 (35.3%) did not plan to be pregnant in a near-future. In the respondents, 292 (17.6%) were medical staff, and 1371 (82.4%) were the general population.

Knowledge about monogenic diseases and ECS

The total awareness rates of the knowledge about monogenic diseases and ECS in the respondents were low, with 35.7%, 26.1%, 3.3%, 23.3%, 24.1%, 55.2%, and 23.4% for questions Q1–Q7, respectively (Table 2).

Cross analysis of knowledge about monogenic diseases and ECS between the medical staff and general population

Table 2 shows the differences between medical staff and the general population for seven items (Q1–Q7). The awareness rate of every item was higher for medical staff compared to the general population. Six questions had significant differences ($P < 0.05$) but Q3 did not ($P > 0.05$).

Comparison of awareness rates for different educational backgrounds

The degree of awareness increased with increased educational level, especially in those with a college degree or beyond (Figure 1). There were significant differences among respondents with different educational backgrounds ($P < 0.05$).

Attitudes toward ECS

Although overall the respondents had little knowledge about monogenic diseases and ECS, most showed a positive attitude. Of respondents, 54.4% suggested that ECS was necessary, and 80.5% wanted more information about monogenic diseases (Table 3). Additionally, 51.7% of respondents thought more pre-test counseling was needed, and 44.8% thought they would follow the provider's advice. Concerning the form of information access, 46.5% selected communicating directly with doctors, 17.9% preferred webinars, 17.3% favored brochures in outpatient waiting areas, 11.4% chose to discuss with a nurse, and 6.8% opted for self-web search.

Comparison of attitudes toward ECS for different educational backgrounds

For people with technical secondary education or beyond, the percentage who thought ECS was necessary increased with educational level (Figure 2). In contrast, the proportion of people who would choose to follow the provider's advice decreased with the educational level rise. For people with technical secondary education or beyond, as the education level increased, more people chose to consult before ECS, and fewer people chose to follow the provider's advice (Figure 2).

The number of diseases, strategy, period, and cost of screening when considering ECS

The questionnaire also asked respondents about the number of diseases to be screened: 58.1% suggested the more, the better; 34.1% preferred the most common ones; and 5.6% thought the less, the better. The remaining 2.2% made no comments. When asked about screening strategy, 83.0% preferred simultaneous screening of couples, while 17% preferred step-by-step screening (one partner is screened first, and then the other if the partner is a carrier). Most respondents chose premarital (43.1%) and

preconception (33.1%) counseling. For an acceptable price of the ECS to respondents, 71% chose less than 1,000 yuan (100 Euro). All of the above are listed in Table 4.

Reasons for rejecting ECS

Among the respondents, 35.2% rejected ECS because the more they knew, the more they were likely to worry, 33.3% rejected ECS for economic reasons, 6.5% for lack of interest, and 25% for other reasons (Table 4).

Discussion

Main findings

One of our study's findings is that although the overall respondents had little knowledge about monogenic diseases and ECS (Table 2), most showed a positive attitude (Table 3). Our cross-analysis showed a gap in knowledge about monogenic diseases and ECS between medical staff and the general population.

Most children with the monogenic disease are born to parents with normal phenotypes and no family history. Most of these couples are unaware of this risk, as carrier status does not affect one's health, and in most cases, the birth of an affected child is highly unexpected(Henneman et al. 2016). Most monogenetic diseases have severe symptoms, such as spinal muscular atrophy, thalassemia, phenylketonuria, etc. Expanded carrier screening for monogenic diseases refers to couples' understanding of their carrying status of some recessive monogenic diseases through genetic testing during the preparation of pregnancy and early pregnancy(Henneman et al. 2016; van der Hout, Dondorp, and de Wert 2019). The core significance of ECS is to help couples make better reproductive decisions and reduce congenital disabilities(van der Hout, Dondorp, and de Wert 2019; Josephi-Taylor et al. 2019).

Our survey showed that the public had little knowledge of monogenic diseases, which will make it challenging to implement ECS. If a patient has little knowledge about ECS, their doctor needs more time for counseling. Benn et al. reported that only one-third of providers were comfortable with pre-test counseling, and less than 25% were satisfied with reviewing results. The main concerns included the time needed for counseling and coordinating follow-up studies and comfort with counseling after a positive result(Benn et al. 2014). A recent study reported that the lack of comfort with ECS counseling and varying beliefs surrounding ECS continue to hinder its utilization(Briggs et al. 2018).

Although the overall awareness is low, our cross-analysis showed that medical staff had a significantly higher degree of awareness compared to the general population. Compared with the general population, medical staffs are more likely to understand the knowledge related to ECS. ECS pre-test education can be carried out by medical staff who are not qualified for genetic counseling, including obstetrician-gynecologists and nurses in the department of Obstetrics and Gynecology. Not all obstetricians and

gynecologists are qualified for genetic counseling, but they have the most access to people who may need ECS. In many cases, obstetricians and gynecologists do not offer patients carrier screening due to a lack of confidence and knowledge concerning genetics(Wilkins-Haug et al. 2000). As genetic technologies evolve and are more incorporated into clinical practice, medical staffs' knowledge is essential. ECS training for medical staff, especially obstetrician-gynecologist and nurse in the department of Obstetrics and Gynecology, can reduce the workload of genetic counseling.

Although the overall respondents had little knowledge about monogenic disease and ECS, most showed a positive attitude (Table 3). This is consistent with the findings of several studies(Facio et al. 2013; Clift et al. 2015; Schneider et al. 2016; Kraft et al. 2018; Poppelaars, Cornel, and Ten Kate 2004). Those with a positive attitude would like to learn more about ECS. Although they may not necessarily choose ECS, learning more about ECS can help them determine if ECS will benefit them.

The main limitation of pre-test counseling for ECS is that it is impractical to thoroughly discuss all the diseases and conditions included in the panel. This is in contrast to pre-test counseling for classical carrier screening programs, which provides information regarding the natural history, detection rates, and prior and posterior carrier probabilities of a limited number of diseases. Thus, the use of ECS necessitates modification of this model(Lazarin and Goldberg 2016).

Although highly educated people had more knowledge of ECS than less-educated people, they seemed more eager to learn when asked if they would like to know more background or get more consultation. In our data, highly educated people were more likely to choose "necessary" (they wanted more information before making a decision); however, less-educated people were more likely to choose "follow the provider's advice" (indicating passive acceptance). This is consistent with previous research(Kahana et al. 2009). The provider's personal opinion is critical to the people who tended to follow the provider's advice. Especially for complex consultations such as ECS, it is time-consuming to achieve fully informed consent. Even highly educated people may not be able to understand ECS through consultation fully. The final choice may be related to the provider's preference.

Some findings in our study were consistent with the recommendations of ACOG, suggesting that carrier screening and counseling should ideally be performed before pregnancy('Committee Opinion No. 691: Carrier Screening for Genetic Conditions' 2017); in our study, most respondents chose premarital (43.1%) and preconception (33.1%). ACOG also suggested concurrent screening for the patient and her partner if there are time limitations for decisions about prenatal diagnostic evaluation('Committee Opinion No. 691: Carrier Screening for Genetic Conditions' 2017). In our survey, 83.0% preferred the simultaneous screening of couples.

Strengths and limitations

The strengths of our study include that the survey was anonymous and not talking about sensitive topics. It is very likely that participants gave accurate answers without fear of exposing their identity. Thus, we

avoided the social desirability bias (obtaining socially accepted answers). Furthermore, the survey was distributed nationally, giving a wide geographic distribution of thoughts and beliefs. One limitation is that the national survey population is not evenly distributed geographically, which affects the representativeness of the sample. The second limitation is that our online survey is voluntary, so there is a volunteer bias. The third limitation is that all the questions were pre-set in the answers' scope, thus limiting the respondents' answers and may omit some detailed and in-depth information. For example, among the reasons for rejecting ECS, 25% of the respondents chose "other reasons" due to the limited options we provided. Given that the survey was electronically distributed, the responses could not be clarified.

Conclusion

Although the public had little knowledge about monogenic disease and ECS, most of them showed a positive attitude. Our cross-analysis showed that medical staff had more knowledge compared to the general population. Pre-test education for ECS can be carried out by medical staff who are not qualified for genetic counseling. ECS training for medical staff, especially obstetrician-gynecologist and nurse in the department of Obstetrics and Gynecology, can reduce the workload of genetic counseling.

Abbreviations

ECS: expanded carrier screening; NGS: next-generation sequencing; ACOG: The American College of Obstetricians and Gynecologists

Declarations

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Funding Statement

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Availability of Data and Materials

All data generated or analyzed during this study are included in this article.

Conflict of Interest:

The authors declare that they have no conflicts of interest to report regarding the present study.

Authors' contributions

Study conception and design: Jing Yang, Min Chen; data collection: Jing Yang, Min Chen, Heli Wu, Wei Shen, Jianmei Han, Yuxia Fu, Jimei Sun, Wenyan Wu; analysis and interpretation of results: Jing Yang, Min Chen;

draft manuscript preparation: Jing Yang, Min Chen. All authors reviewed the results and approved the final version of the manuscript.

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Tables

Table 1. Demographic characteristics of the study population

Characteristic	N (%)
Gender	
Female	1490 (89.6)
Male	173 (10.4)
Marital status	
Single	90 (5.4)
Married	1550 (93.2)
Divorced	22 (1.3)
Widowed	1 (0.1)
Age (years)	
18-25	141 (8.5)
26-34	926 (55.7)
35-44	483 (29.0)
45-50	113 (6.8)
Educational level	
No education or primary education	14 (0.8)
Lower secondary education	193 (11.6)
Technical secondary education	135 (8.1)
Upper secondary education	120 (7.2)
College education	389 (23.4)
Undergraduate education	646 (38.8)
Graduate education	166 (10.0)
Number of children	
None	672 (40.4)
One or more	991 (59.6)
Family history of a genetic condition	
Yes	149 (9.0)
No	1514 (91.0)
Considering a near-future pregnancy	
Currently pregnant (partner or self)	971 (58.4)
Yes	105 (6.3)
No	587 (35.3)
Medical staff or not	
Yes	292 (17.6)
No	1371 (82.4)
Total	1663 (100)

Table 2. Cross analysis of knowledge about monogenic diseases and ECS between medical staff and general population

Questions	General population	Medical staff	Total	P value
Q1. Have you ever heard of monogenic diseases?				
No	1018(74.3)	52(17.8)	1070(64.3)	<0.05
Yes*	353(25.7)	240(82.2)	593(35.7)	
Q2. Diabetes and hypertension have a familial tendency, whether they belong to monogenic diseases?				
Yes/Not sure	1097(80.0)	132(45.2)	1229(73.9)	<0.05
No*	274(20.0)	160(54.8)	434(26.1)	
Q3. What is the combined incidence of monogenic diseases?				
Wrong (1/10 or 1/1000) or Not sure	1331(97.1)	277(94.9)	1608(96.7)	>0.05
1/100*	40(2.9)	15(5.1)	55(3.3)	
Q4. Can you distinguish dominant monogenic diseases from recessive monogenic diseases?				
No	1130(82.4)	145(49.7)	1275(76.7)	<0.05
Yes*	241(17.6)	147(50.3)	388(23.3)	
Q5. What's the probability of having an affected child in each pregnancy when couples are both carriers for the same AR disorder?				
Wrong (50% or 100%) or Not sure	1122(81.8)	140(47.9)	1262(75.9)	<0.05
25%*	249(18.2)	152(52.1)	401(24.1)	
Q6. Whether measures can be taken to avoid having an affected child in each pregnancy when couples are both carriers for the same AR disorder?				
No/Not sure	686(50.0)	59(20.2)	745(44.8)	<0.05
Yes*	685(50.0)	233(79.8)	918(55.2)	
Q7. Have you heard of expanded carrier screening?				
No	1118(81.5)	156(53.4)	1274(76.6)	<0.05
Yes*	253(18.5)	136(46.6)	389(23.4)	

The correct answer and the answer indicating "know" are marked with *

Table 3 Attitudes toward ECS

Questions	N (%)
Whether it is necessary to screen people with monogenic diseases to prevent the birth of children with monogenetic genetic diseases?	
Necessary	905(54.4)
Unnecessary	12(0.7)
Follow the provider’s advice	577(34.7)
Not sure	169(10.2)
Would you like to know more about monogenic diseases?	
Yes	1339(80.5)
No	324(19.5)
Do you need more counseling before selecting for expanded carrier screening?	
Yes	860(51.7)
No	58(3.5)
Follow the provider’s advice	745(44.8)
In what form do you wish to obtain more information about monogenic diseases and ECS?	
Communicate directly with doctors	774(46.5)
Brochures in outpatient waiting area	288(17.3)
Webinar	298(17.9)
Self-web search	113(6.8)
Discuss with a nurse	190(11.4)

Table 4 The number of diseases, strategy, period, and cost of screening when considering ECS

Questions	N (%)
If you are screening for carriers of a single gene, what is the number of diseases you want to screen for?	
The more the better	967(58.1)
Screen only the most common ones	567(34.1)
The less the better	93(5.6)
None	36(2.2)
Which screening strategy do you prefer?	
Simultaneous screening of couples	1380(83.0)
One partner is screened first, and then the other if the partner is a carrier	283(17.0)
When do you think it is the best time to screen for monogenetic diseases?	
Neonatal or childhood	234(14.1)
Student hood	83(5.0)
Premarital	717(43.1)
Preconception	551(33.1)
After pregnancy	78(4.7)
Acceptable price range for screening single gene carriers (CNY)	
<1000	1180(71.0)
1000-1500	274(16.5)
1500-2000	117(7.0)
2000-2500	92(5.5)
Why do you refuse to be screened for a single genetic disease carrier?	
The more you know, the more you may worry	585(35.2)
Economic reasons	554(33.3)
Not interested	108(6.5)
Other	416(25.0)

Figures

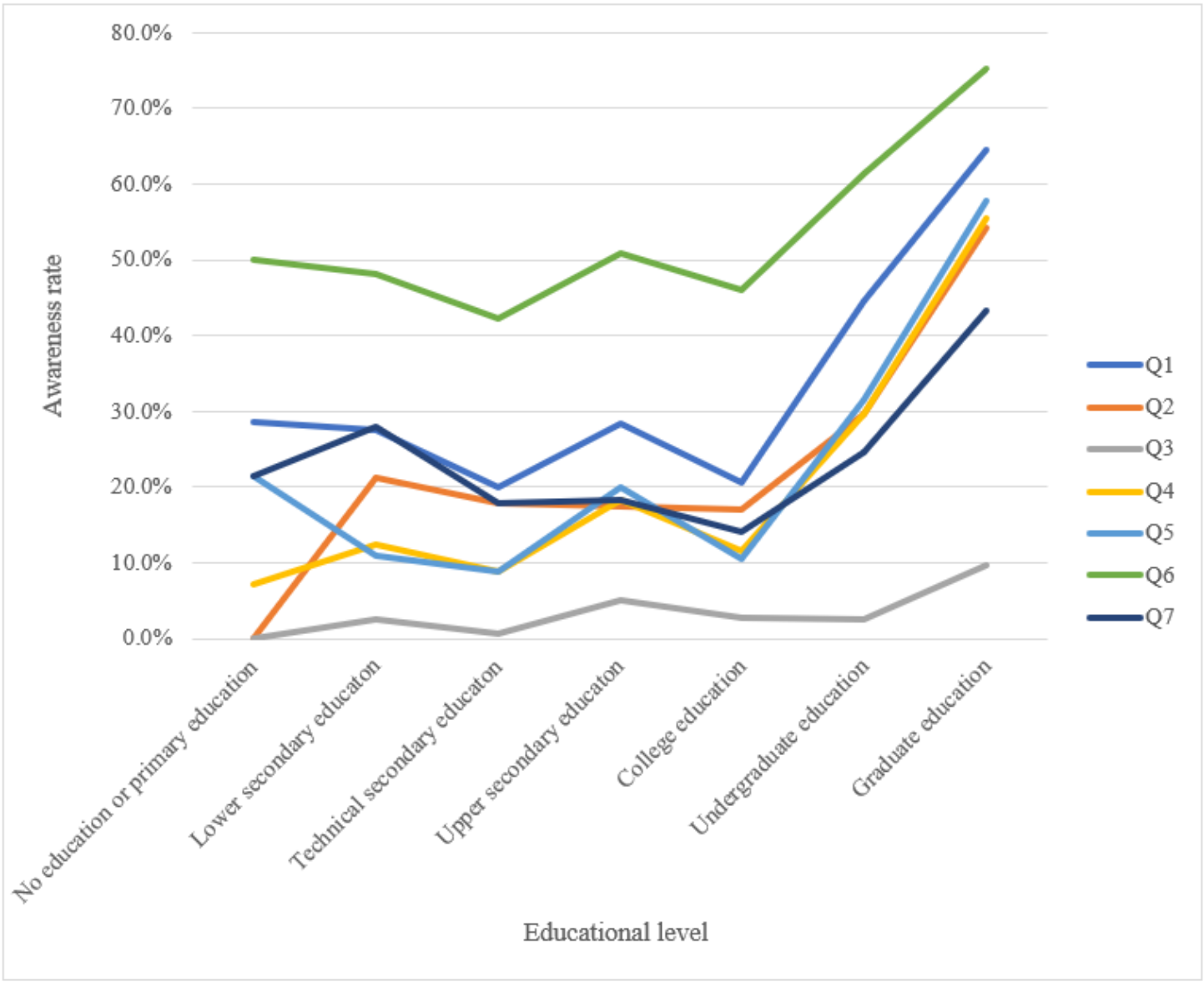

Figure 1

Comparison of awareness rate of different educational backgrounds (P<0.05)

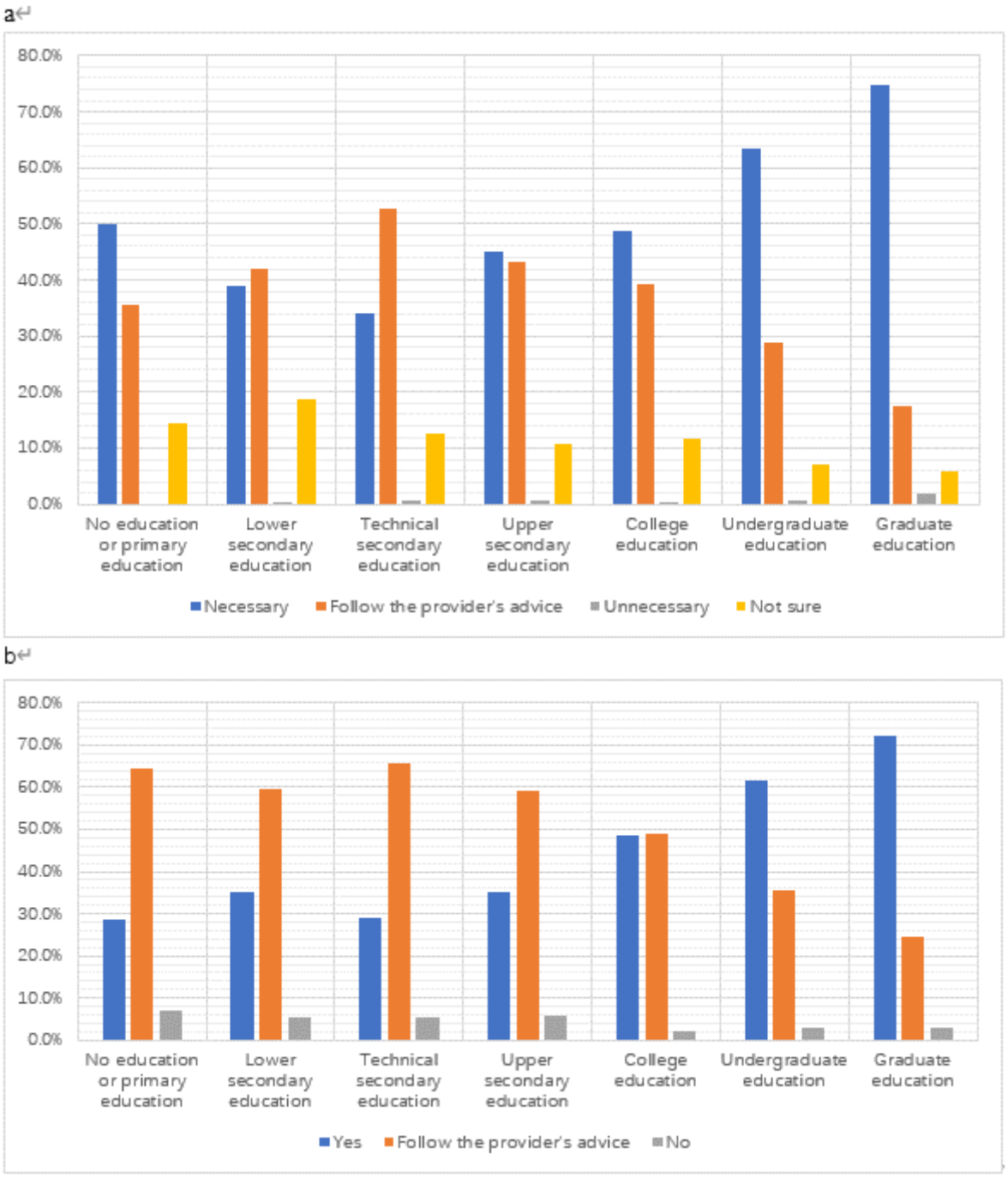

Figure 2

Comparison of the attitudes of different educational backgrounds toward ECS a. Whether it is necessary to screen people with monogenetic diseases to prevent the birth of children with monogenetic genetic diseases? b. Do you need more counseling before selecting for expanded carrier screening?

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1Questionnaire.docx
- AdditionalFile2thestudypopulationdistributionmap.docx