

RESEARCH ARTICLE

Targeting the gut microbiome: A brief report on the awareness, practice, and readiness to engage in clinical interventions in Qatar

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ABSTRACT

Background: There has been a growing global interest in the role of gut microbiota in the pathogenesis of diseases and the potentials of targeting the microbiome in clinical interventions. Very few clinical studies in Qatar focused on gut microbiome. This study aimed to assess the awareness of healthcare professionals, scientists, and the general public on the role of gut microbiota in health and diseases and, more specifically, in disorders of the gut – brain axis such as neurodevelopmental disorders (NDDs) or gastrointestinal (GI) disorders. It also aimed to evaluate the readiness of the population to engage in clinical trials involving dietary interventions or fecal transplants.

Methods: A total of 156 participants were recruited to answer questionnaires—from healthcare professionals and scientists (HSs; n = 44) and the general public (n = 112). Participants from the general public self-reported their diagnosis of NDDs—autism or attention deficit hyperactivity disorder (n = 36)—or GI diseases or disorders (n = 18) or as having none of them (n = 58). Two questionnaires for HSs and for the general public were distributed, and basic descriptive and statistical analyses were conducted using the Fisher's exact test.

Results: Among the participating HSs, 95% admitted that they had minimum to no knowledge on the role of gut microbes in health and diseases, and only 15.9% felt that their peers were knowledgeable about it. Nevertheless, 97.7% of HSs thought that gut microbiota should be considered when devising treatment plans as 79.1% believed that gut dysbiosis is involved in the pathogenesis of diseases. For the

general public, 54% stated that they have read about studies on the potential benefits of microbes in the prevention, treatment, and management of diseases, with a higher proportion of them belonging to the GI group ($p=0.0523$). The GI group was also more aware of the existence of the use of fecal transplants for treating their condition ($p=0.01935$). Awareness was also reflected in participants' attempts to engage in dietary changes, as 40% tried a dietary intervention, which has noticeably changed their or their child's symptoms. This study reported a highly significant association between being exposed to multiple antibiotic courses before three years of age and being part of the NDD group ($p=0.0003$). Public readiness to engage in interventions that target the gut microbiome, such as intensive dietary interventions or even fecal transplants, was perceived by HSs to be lower than what was stated by the public, with 87.96% of public being ready to engage in intensive dietary interventions and 66.98% in fecal transplants. Conclusion: The study revealed that the role of gut microbes in health and diseases, and especially through the gut – brain axis, is still unclear in both the scientific community and general public. While acknowledging the importance of gut microbes, the lack of information regarding the link between lifestyle and gut microbes is considered to hold the public in the precontemplation/contemplation stages of the transtheoretical model of behavioral change. An interdisciplinary approach to new knowledge produced by microbiome studies is needed to run awareness campaigns and continue professional development activities on the benefits of lifestyle-based modulation of gut microbiome, thus engaging the general public in lifestyle changes and facilitating clinical research in human microbiome investigations in Qatar.

Keywords: Microbiota, Awareness, dietary intervention, fecal transplants, Autism, gastrointestinal, health

INTRODUCTION

Health sciences are experiencing a paradigm shift with the growing interest in gut microbiome.¹ With recent technological advancements and expanded funding for human microbiome research such as the ones provided by the National Institutes of Health (NIH) through their extramural funding, databases are flooded with new data and information regarding the association of gut microbes with diseases.² Today, evidence is pointing at important roles of gut microbes in metabolic diseases,^{3–6} neurological

diseases,^{7–9} neuropsychiatric and neurodevelopmental disorders (NDDs),^{10,11} autoimmune diseases,^{12,13} cardiovascular diseases,^{14,15} and cancers.^{12,16} Many have tried eliciting 'microbial prints' for diseases, and associations have been described at the phylum and specie levels with some diseases or disorders. However, no consensus was reached as to which microbial composition can be salvatory for a disease.

A study by the NIH Human Microbiome Portfolio Analysis Team² reviewed the human microbiome projects ran over the past decade and concluded that there is no 'one size fits all' strategy for microbiome-based interventions for treating diseases. This is probably the reason why several teams across the globe have started clinical interventions that aim to correct the dysbiosis associated with a large spectrum of diseases. There are two types of trials as follows:

- Lifestyle changes: mostly dietary, with a large panel of diets and supplements tested such as plant-based diets and probiotics^{17–20}
- Fecal transplant: an acute method for correcting gut dysbiosis by transferring gut microbes from feces of a healthy donor to the gastrointestinal (GI) tract of a patient^{21–24}

As lifestyle medicine is becoming a novel medical specialty, there is growing evidence that the mechanisms by which lifestyle changes can benefit health and reverse diseases are linked to the modulation of gut microbiome.^{25–29}

Targeting the gut microbiome with clinical interventions has become a novel approach for treating diseases, and an increasing number of studies are being registered worldwide. However, only a small number are being performed in the Middle East and none in the Gulf region.^{30,31}

In 2017, only nine studies containing the terms '(microbiota OR microbiome) AND Qatar' were recorded on the PubMed database (Figure 1), whereas more than 10,000 were being published worldwide, with focuses on the multiple roles of the gut microbiome in the pathogenesis of diseases, including disorders along the gut – brain axis. This gap in Qatar's contribution to scientific knowledge around microbiome and microbiota was hypothesized to be reflective of a knowledge gap among the healthcare and scientific community and/or the general public, who were not ready to engage in clinical studies.

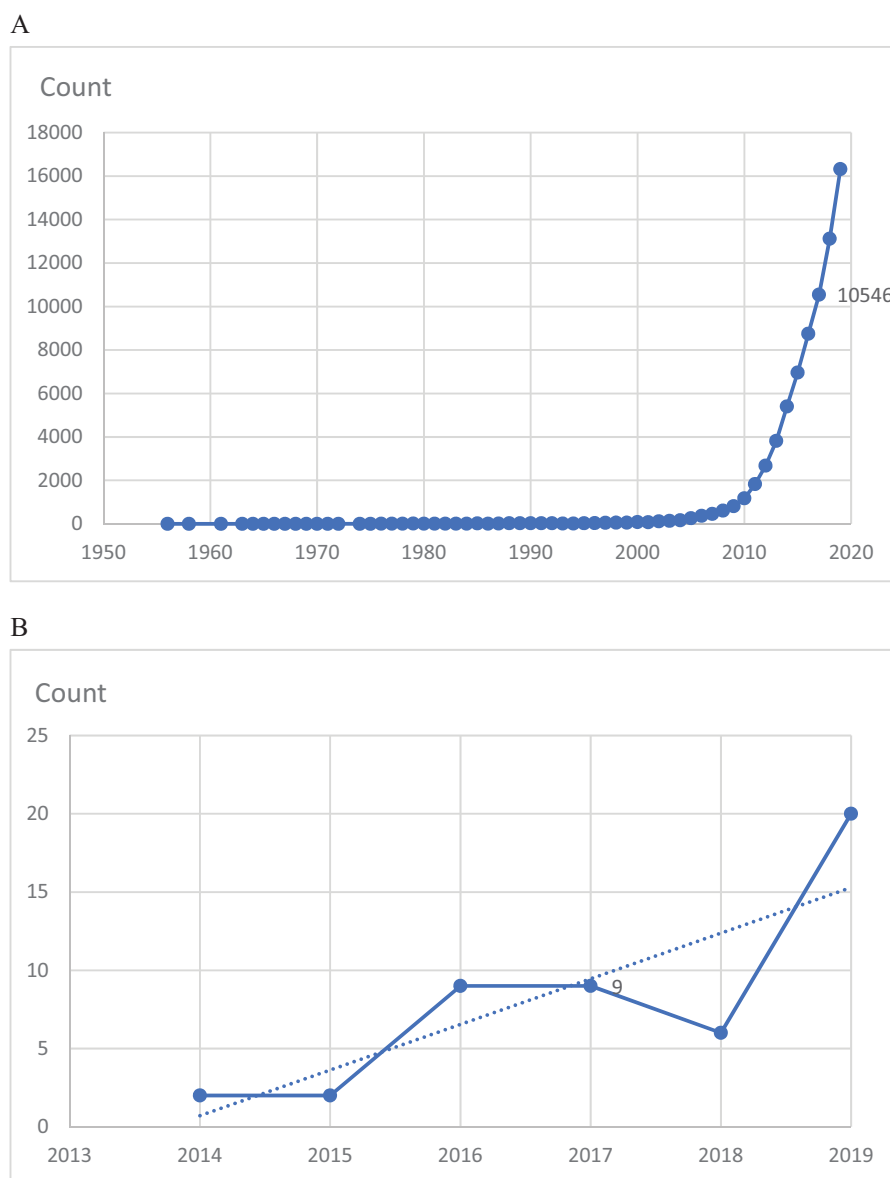


Figure 1. The increasing number of publications on microbiota/microbiome (A) worldwide and (B) in Qatar. The MeSH formula "(microbiome OR microbiota)" was used on PubMed database with no other filter for worldwide, and the MeSH formula "(microbiome OR microbiota) AND Qatar" was used for Qatar’s publication counts. The figure depicts the number of counts per year.

As the number of children with NDDs was increasing in Qatar, local clinical microbiome studies that focus on this new approach by starting clinical interventions are deemed important to target and analyze changes in the gut microbiome. However, some challenges are usually reported in studies conducting nutritional research such as the participants' baseline nutritional status, awareness, and motivation and engagement. For this reason, we have launched a pilot study in 2018 that aimed to assess the awareness of healthcare professionals and scientists (HSs) and the

general public on the role of gut microbes in health and diseases and, more specifically, in diseases of the gut – brain axis such as autism spectrum disorders (ASDs), attention deficit hyperactivity disorders (ADHDs), and GI diseases including inflammatory bowel diseases (IBDs; Crohn’s disease and ulcerative colitis), irritable bowel syndrome (IBS), and celiac disease, which are all under GI disorders.

Our study also aimed to evaluate the readiness of the population to engage in clinical trials involving dietary interventions or fecal transplants.

Therefore, this paper describes the state of awareness and readiness of both the general public and scientific community, which are important prerequisite when devising future plans for clinical studies involving interventional or observational microbiome studies in Qatar that involve individuals with the conditions under study. This study, by providing an overview of the state of knowledge and awareness of HSs, points at knowledge gaps that could lead to practice gaps. In addition, by investigating on the same among the public and on their readiness to engage in clinical interventions, we can draw nutritional baselines and list some of the important challenges to consider in future clinical studies.

We will conclude on the feasibility of running dietary interventions among children with ASDs or IBDs in Qatar and the need and benefits of running public awareness campaigns on the role of the gut microbiota in NDDs and health and diseases in general.

METHODS

Study Design and Questionnaires

Two questionnaires were designed for HSs and the general public. Both questionnaires were distributed simultaneously to both communities and during the same period (between February and June 2018), which makes this an observational cross-sectional study.

Questionnaires were prepared using Google forms in both the English and Arabic languages, and links were generated for distribution by emails and social media asking participants to answer one or the other questionnaire depending on which community they belong to (HS or public). Alternatively, questionnaires were proposed to participants on paper. All HSs (n = 44) answered online, and 62 of 112 participants from the public answered on paper (50 answered online). Both online and paper answers were analyzed together.

Details of the questions asked for each questionnaire are mentioned progressively in the Results section.

Eligible participants were residents of Qatar who were over the age of 18 years and spoke English or Arabic. Parents were asked to fill survey for their minor children who fit in one of the three group studies (NDD, GI, or control). The questionnaire was developed based on the study objectives, and the institutional review board approved the study.

Recruitment

Links to online forms were distributed by email and social media across Qatar between February and June 2018. Some paper formats were distributed on the occasion of seminars in Qatar, and in this case, data collected were manually entered into the database.

Sample size and heterogeneity

A total of 44 HSs answered the HS questionnaire: 20 were involved in treating patients with ASD, ASHD, or IBD, 22 were not involved in treating patients with the previously mentioned disorders, and 2 did not answer this question.

A total of 112 participants from the general public represented the various ethnicities in Qatar (Table 1). The most represented ethnicity in each group was as follows: Middle Eastern (38.9%) for the NDD group, Caucasian (50%) for the GI group, and Middle Eastern (39.7%)/Caucasian (36.2%) for the control group.

This study grouped individuals with NDDs together under the label NDD and those with GI diseases or disorders under GI.

The repartition per condition among the participants from the public was as follows:

- NDD: 36 had ASD or ADHD.
- GI: 18 had an IBD, IBS, or celiac disease.

Table 1. Recruited participants from the general public per ethnic group.

Primary condition	Missing answer	Caucasian	African	Middle Eastern	South Asian	South East Asian	None/Mixed	Total
Control	0	21	1	23	5	7	1	58
NDD	4	2	1	14	9	4	2	36
GI	2	9	0	6	1	0	0	18
Total	6	32	2	43	15	11	3	112

NDD, neurodevelopmental disease; GI, gastrointestinal disease.

- 58 had none of the above disease or disorder and were labelled as 'controls.'
- 6 did not mention their condition.

Analysis

Descriptive analysis was performed using the International Business Machines Corporation - Statistical Package for the Social Sciences or IBM-SPSS software (IBM Corp, Armonk, NY, USA). Comparisons of population proportions were conducted using the Fisher's exact test—in R statistical package—at 95% confidence interval (CI).

RESULTS AND DISCUSSION

Awareness of the importance of the gut microbiome in health and diseases

HSs

Of participants, 84.1% answered no, and only 15.9% thought that the HS community was knowledgeable to the question "Do you feel that healthcare professionals in Qatar are knowledgeable about the role of the gut microbiota in ASD, ADHD, IBD?" HS participants were also asked how much they knew about the role of the gut microbiota in diseases in general, and more than 95% admitted that they had minimum to no knowledge about it.

Interestingly, 97.7% of HS thought that the gut microbiota should be considered when devising treatment plans. This apparent contradiction reveals the unprecedented surge in microbiome studies that happened in the last few years (Figure 1), and its medialization might have actually imprinted minds in such a way that HS know that the gut microbiome plays important roles without fully understanding its mechanisms.

Indeed, 79.1% of HS participants believed that gut dysbiosis is involved in the pathogenesis of diseases of developed countries, including not only ASD, ADHD, and IBD (as stated in the questionnaire) but also diabetes, obesity, and other autoimmune diseases.

Several studies have investigated the impact of the mode of delivery in infant's gut microbiome.^{32–36} Curran et al.³⁷ first indicated in a meta-analysis that the gut microbiota of infants born via cesarean section (C-section) differs significantly from those infants born naturally. In another study, the same team observed that the increase in the observed risk of developing ADHD associated with C-section in siblings might actually be due to confounding factors,

as it was observed only in emergency C-sections.³⁸ Tribe et al.³⁴ suggested that breastfeeding is an important factor to consider, especially in women who deliver via C-section as they often report breastfeeding issues with early cessation. Several confounding factors are progressively pointing to specific factors linked to C-section, such as the absence of labor or type of antibiotherapy used during C-section and susceptibility to develop candidiasis leading to early breastfeeding cessation.^{36,39}

In our study, 84.1% of HS agreed, based on their professional experience, on the importance of the role of the gut microbiota and the mode of delivery in the pathogenesis of ASD or IBD.

Participants from the general public were asked how they were born, and the results are depicted in Figure 2. Although our sample size was relatively small, and no definite conclusion can be drawn (Fisher's exact test *p* values were 0.3861 and 0.24, respectively, for NDD and GI), the trend observed in the higher proportion of C-section among the ASD population is worth mentioning and deserves further investigations in a local cohort while including other possible confounding factors such as presence of labor, candidiasis, and duration of breastfeeding.³³

General public awareness

A growing number of studies have highlighted the potential of beneficial microbes in the prevention, treatment, and management of diseases, including ASD and IBD, in both preclinical and clinical studies.^{40–45} We asked our participants if they had ever heard of studies on the role of gut microbes in health and diseases, and 54% said that they did (data not shown), with a higher proportion of them being from the GI group (Fisher's exact test *p* value was 0.0523; odds ratio: 0.29; Figure 3A). Indeed, it makes sense that individuals with GI diseases or disorders are more likely to encounter and read scientific updates and studies on the microbiome by simply making searches on their own condition, which is already a GI disease. Similarly, they are also the ones who were aware, at a significantly higher proportion than the control, of the existence of clinical trials involving fecal microbiota transplants for their disease (Fisher's exact test *p* value was 0.01935; significant at $p < 0.05$, odds ratio: 0.226, 95% CI: 0.05359792 – 0.82876599; Figure 3B). This suggests that the chance of belonging to the GI group when one is aware of the existence of fecal transplants is 0.226 than for someone who is not.

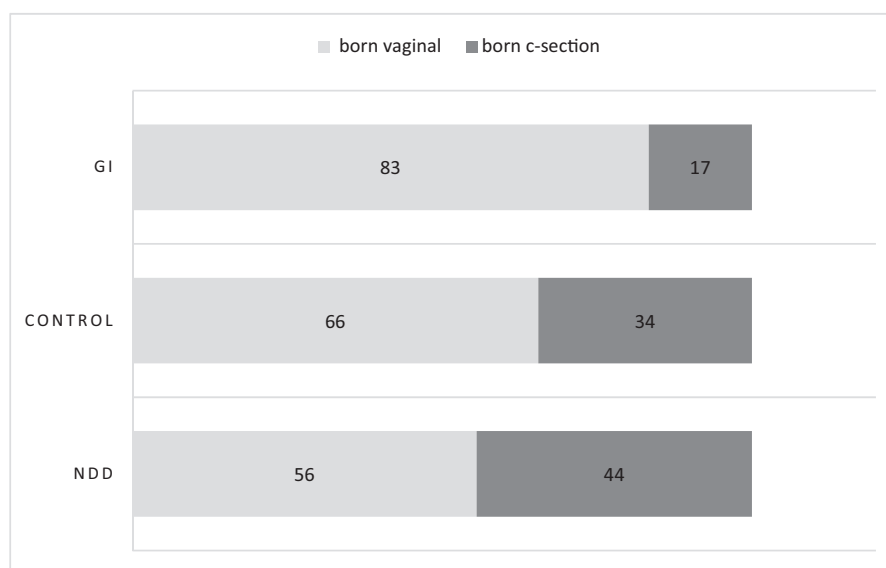


Figure 2. Mode of delivery among each group. C-section, cesarean section; GI, gastrointestinal; NDD, neurodevelopmental disease.

On the contrary, this result suggests that gut – brain axis studies might need to be popularized before the general public could understand and evaluate the importance of gut microbes in neurological diseases and neuropsychiatric disorders. At the time of the investigation, only 7 of 36 participants in the NDD group had heard about fecal transplant use for ASD, although a trial was already existing and recorded on the clinicaltrials.gov database.⁴⁶

However, the clinical trial conducted by Kand et al.²¹ revealed unprecedented results on the benefits of fecal transplants in autism, and the number of studies on the role of microbiota in Qatar and worldwide is increasing (Figure 1). Therefore, we hypothesize that the ASD community awareness about the role of microbiota in ASD could be currently higher than what is described in this paper, which is based on data collected in 2018.

To conclude about awareness, the role of gut microbes in health and diseases, and especially through the gut – brain axis, is still unclear to both the scientific community and general public. However, since 2018, several clinical research studies on gut microbiome were awarded in Qatar, yielding several publications, which must have probably increased awareness since then. Yet, the first to have been exposed to this new set of information were probably individuals who suffered from a GI disorder or disease as GI diseases can easily be associated with gut microbes.

An interesting study by Greenhough et al.⁴⁷ highlighted the complexity of microbiome studies and how an interdisciplinary approach is fundamentally needed to raise awareness, involving social sciences and humanities, which could actually facilitate clinical studies and advances in microbiome studies. Greenhough et al.⁴⁷ proposed an agenda that is a great source of inspiration for not only HSs but also members of other disciplines to tackle eight priorities on microbiome research, such as the impact of this new knowledge on healthcare governance and practice and how it affects agricultural practices, social behaviors, and, consequently, the environmental microbial homeostasis and health. With the emergence of severe acute respiratory syndrome coronavirus 2, the relationships of humans and microbes have been questioned and been deeply affected by the use of chemicals such as sanitizers (with observation increase in resistance to chemicals in hands), microbiome convergence, and biodiversity decrease in some food plants.^{48,49}

Clinical practice

At the time of the investigation (2018), only 15.9% of the HSs who participated said that they have considered the implications of the gut microbiota in NDD or GI disorders during their practice. Approximately 31% said that they do discuss the role of the gut microbiome with their patients with an NDD or GI disorder. In addition, 47.7% of the same participants

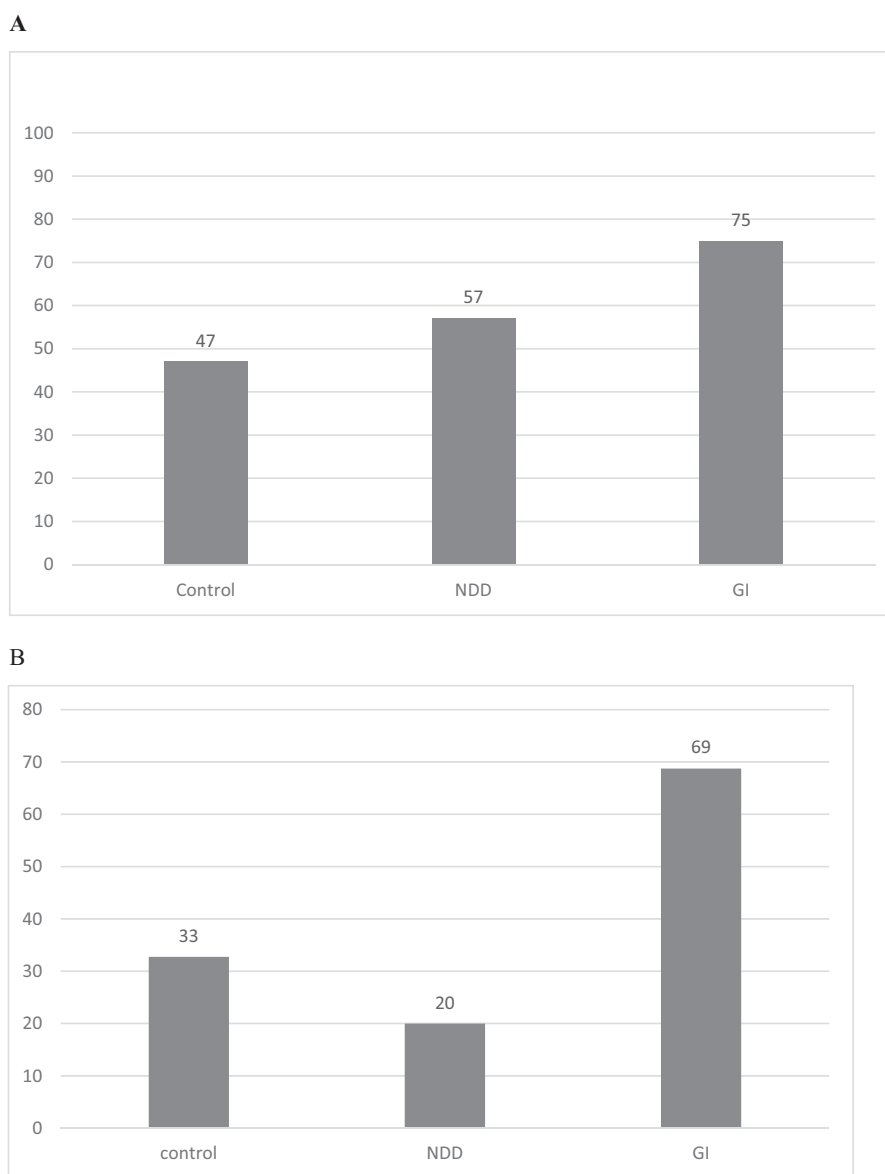


Figure 3. Public awareness. (A) Proportion of participants per group who have read out studies on the role of gut microbes in health and diseases. (B) Proportion of participants per group who were awareness of the existence of clinical trials using fecal transplants. GI, gastrointestinal; NDD, neurodevelopmental disease.

referred their patients to nutritionists or dieticians only if they have a GI disorder, whereas 13.6% systematically do it when they devise treatment plans for ASD, ADHD, or IBD. Interestingly, 53% of participating HSs reported having seen positive effects on their ASD/IBD patients after introducing a dietary change.

This study compared the responses from HS with those obtained from the public. Participants from the general public were asked whether they have tried changing their diet and noticed significant changes in symptomatology. Approximately 40% of participants have tried a dietary intervention, which, according to them,

have noticeably changed their or their child’s symptoms. Among those, 16% were from the NDD group. Individuals from the NDD group were more likely to engage in a dietary intervention and noticed improvements than those from the control group (53% of NDD, 31% of controls, and 56% of GI). Fisher’s exact test p value was 0.0505, odds ratio: 2.45, 95% CI: 0.9651906 – 6.3987124. The result is not significant at $p < 0.05$ but is significant at $p < 0.1$, which highlights the importance of the need to further investigate the role of diet in the modulation of the gut microbiome and treatment of diseases.

Although dysbiosis can occur at any period of life, a critical window has been described in microbiome studies, during which any alteration of the gut microbiota composition could lead to sustained dysbiosis through life, thus playing an important role in the pathogenesis of diseases.^{50,51} On the other hand, recent studies have explored antibiotic misuse in Qatar and revealed that misconceptions about antibiotics are common in the population, which lead to extensive use of antibiotics when they are not needed.^{52–54}

We were interested to know whether our participants recall having been exposed to multiple courses of antibiotics before their third-year anniversary. Fisher's exact test was used to compare proportions of the control versus NDD groups who were exposed (or not) to multiple courses of antibiotics before three years old as self-reported by participants. The results in Figure 4 indicate a highly significant difference as the p value was 0.0003, odds ratio 0.19, and 95% CI 0.06703852–0.51146584. The result of this study suggests that the chance of belonging to the NDD group when one was exposed to antibiotics at an early age is 0.19 than for someone who was not. However, this result needs to be further explored using a bigger sample size. For the GI group, Fisher's exact test p value was 0.1319 (odds ratio 0.41) and was not significant (Figure 4).

This important result about the role of early antibiotic exposure in the pathogenesis of autism has been reported by other studies.⁵⁵ Two metaanalyses

concluded that the data are conflicting and that the analyses need to also consider prenatal antibiotic exposures as strong associations.^{56,57}

Relocation

Some studies mentioned that relocation to a new country was a factor that was associated with diseases such as ASD,⁵⁸ pointing at the possible role of lifestyle habits.⁵⁹ We have asked participants from the public whether their (or their child's) symptoms increased after their relocation to Qatar, and 75.4% indicated that symptoms did not noticeably increase, whereas 24.6% affirmed that they did. This question was not investigated among healthcare professionals.

Readiness to engage in clinical interventions targeting the gut microbiome

On the other hand, participants from the public were asked few questions about their lifestyle habits, which were expected to reflect not only their awareness but also their readiness to engage in clinical interventions.

Processed food

Growing evidence pointed the role of diet in shaping the gut microbiome and consequently the pathogenesis of diseases.^{26,28,60–64} The participants were asked about the proportion of processed food they eat (mentioned to them: bread, potatoes, rice, cookies, pastries, sweets, etc.). Interestingly, although previous data showed different awareness levels between the three groups, no significant difference

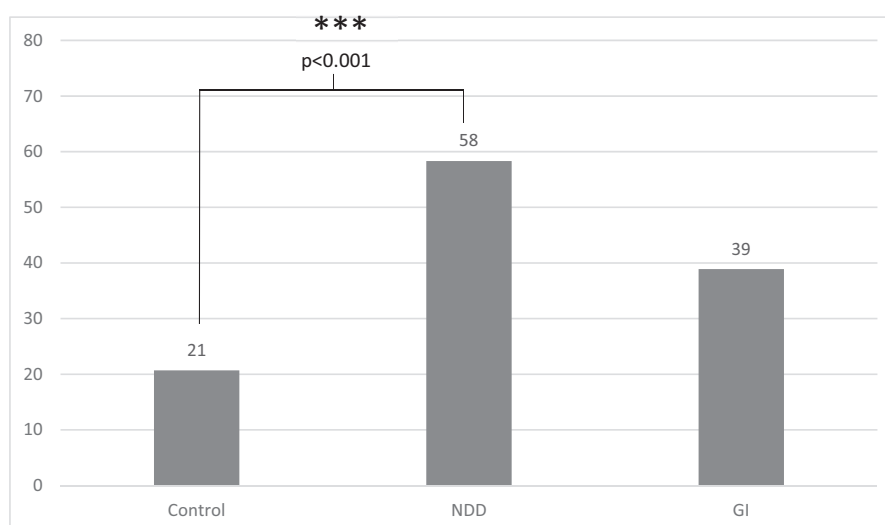


Figure 4. Proportion of participants per group who reported that they (or their child) were exposed to multiple courses of antibiotics before three years old. GI, gastrointestinal; NDD, neurodevelopmental disease.

was found between those groups when it comes to their diet type (Fisher’s exact test *p* value was 0.3931 for NDD vs. control and 0.7438 for GI vs. control; Figure 5A).

This apparent contradiction is explained according to the principles of the transtheoretical model of behavioral change that participants, although aware of the importance of gut microbes in health and diseases, are still in the precontemplation stage.⁶⁵ The reason might be that they do not fully understand the links between lifestyle, gut microbes, and health.

Probiotics

Probiotics have been recognized for their beneficial effects on health, and they are used as potential dietary supplements.⁶⁶ Probiotic health benefits are not only limited to the intestinal tract but also include the amelioration of many diseases and disorders including cardiovascular diseases, diabetes, and neurobiological disorders.^{67–70} Studies showed that probiotics could alleviate some of the symptoms of autism and mood disorders by directly restoring the gut microbiota balance or other ways such as

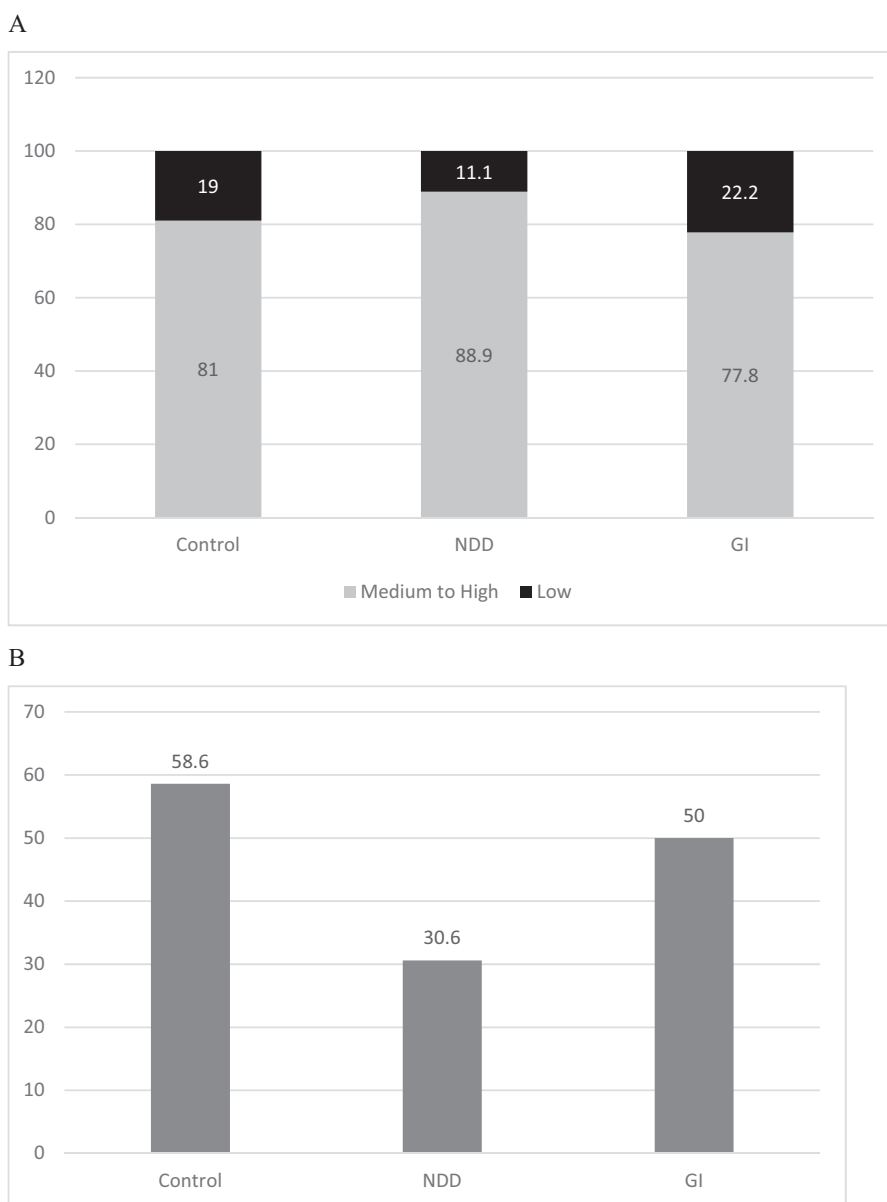


Figure 5. Dietary habits among participants. (A) Proportion of participants per group who had diets low or medium to high in processed food. (B) Proportion of participants per group who regularly consumed probiotics. GI, gastrointestinal; NDD, neurodevelopmental disease.

strengthening the GI barrier through intercellular adhesion tightening.⁷¹ Moreover, over the past decade, an increased public interest was given to the impact of diet and lifestyle choices on health. In this context, several studies reported a potential link between dietary factors and alterations in the epigenome and epigenetic pathways.⁷²

Consumption of probiotics was used in our questionnaire to evaluate participants' awareness on the benefits of probiotics for their condition. Overall, approximately 48% of participants stated that they were consuming probiotics regularly. Interestingly, the proportion of individuals who stated they were regularly consuming probiotics was lower in the NDD and GI groups than in the control group; however, Fisher's exact test *p* value was 0.5914, which is not significant (Figure 5B). A hypothesis would be that regular consumption of probiotics is mostly due to mediatization rather than deep understanding and awareness of the mechanisms of action.

Engaging in clinical interventions

Of healthcare professionals, 95.5% reported that they would consider recommending their patients additional treatment that target the microbiome such as probiotics and dietary plans.

However, only 22.7% of Qatar's healthcare professionals who participated in the questionnaire thought that fecal transplant can be useful for treating ASD or IBD.

Interestingly, a mismatch between the real readiness of the public and the readiness as perceived by professionals was noted. Of HSs, 38.1% thought that families would not be open to clinical trials involving intensive dietary changes, but when the same question was asked to families, 87.96% of public participants stated that they were ready to engage in clinical interventions that involve intensive dietary changes.

In addition, 66.98% of the general public stated that they would even consider participating in fecal transplant trials, whereas 54.8% of healthcare professionals thought that the public would not consider this as an option.

To conclude about readiness, although the participants are aware of the importance of gut microbes in health and disease, these data suggest that overall, participants from the public were in the precontemplation/contemplation stage of the transtheoretical model of behavioral change, in which the patients are

aware but not empowered to make a lifestyle change.⁶⁵ Data suggest that families who deal with ASD or ADHD do not have a clear understanding of the impact of diet and probiotics on the condition, as the NDD group had the highest diet in processed grain-based food and the least intake of probiotics; however, this is not significant because of our sample size. Although this study shall be extended to evaluate the real situation, the public could benefit from popularization of scientific studies in the gut-brain axis.⁷³

LIMITATIONS

Some of the limitations of this study to consider are the relatively small sample size among the HS group (*n* = 44). Conclusions drawn about HSs need to be considered in this context. Nevertheless, the publication counts reported (Figure 1) still reflect a need to raise awareness among this group.

Participants who answered the questionnaire were mostly from the public with 112 participants, which represent 71% of total participants. The study did not investigate whether taking the survey online or on paper had an impact on answers.

It would have been interesting to learn from healthcare professionals what their antibiotic prescription habits are for infants. However, this was not conducted in the study. Further explorations are needed to understand the role of early exposure to antibiotics in the pathogenesis of NDD and GI disorders.

CONCLUSION

As several axes of communication have been found from the gut to other organs than the brain-gut-skin,⁷⁴ gut-liver,⁷⁵ gut-pancreas,⁷⁶ and gut-lung⁷⁷ axes, we believe that instilling the current lifestyle awareness campaigns in Qatar with popularized versions of the latest microbiome studies would be a novel approach to engage the public in lifestyle changes targeting the gut microbiome, thus facilitating clinical studies in this area.

As per the model of behavioral change, raising awareness is not sufficient to engage the population in healthy lifestyle changes, and it is the responsibility of the healthcare provider to discuss the health risks and benefits associated with lifestyle.

This is particularly important as running clinical dietary intervention for the autistic population might be extremely difficult for the following reasons:

- (1) Dysbiosis was described to create a sensation of 'sugar craving' in autistic children and adults with other diseases.^{78,79} Interventions will require important human coaching resources.
- (2) An interventional study would face important regulatory challenges as to how to protect children against child abuse in parents 'forcing' their children to abide by the diet for example.

For these reasons, observational studies might be more effective than interventional ones.

Therefore, raising awareness on the importance of healthy lifestyles and the mechanisms by which they can improve health and reverse diseases could increase

the proportion of individuals of the population who self-engage in healthy lifestyle changes, thus making possible observational microbiome studies and overcoming most challenges cited.

To conclude, this study highlights the needs and benefits of running awareness campaigns and continuing professional development activities on the benefits of lifestyle-based modulation in the gut microbiome.

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