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

Ghizlane Bendriss1,*, Dana Al-Ali1, Ameena Shafiq1, Ibrahim Laswi1, Nada Mhaimeed1, Mohammad Salameh1, Zain Burney1, Krishnadev Pillai1, Ali Chaari1, Dalia Zakaria1, Noha A. Yousri2,3

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 dietary interventions and 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.

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. 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.

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.
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.

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.
Therefore, this paper describes the state of awareness and readiness of both the general public and scientific community, which are important prerequisites 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.

| 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

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 antihisterapy 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 0.0193; 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.
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...
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 symptoms. 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.

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.
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 metanalyses 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
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. 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. 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. 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 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.](image-url)
strengthening the GI barrier through intercellular adhesion tightening. 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.

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. 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.

**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, gut—liver, gut—pancreas, and gut—lung 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:
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.

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.

**FUNDING**

This work was supported by the Qatar National Research Fund. Grant Number: 5727002821.

**REFERENCES**

1. Althani AA, Marei HE, Hamdi WS, Nasrallah GK, El Zowalaty ME, Al Khodor S, et al. Human microbiome and its association with health and diseases. *J Cell Physiol* [Internet]. 2016 Aug [cited 2017 Mar 13];231(8):1688 – 94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26660761

2. Team NHMPA. A review of 10 years of human microbiome research activities at the US National Institutes of Health, Fiscal Years 2007-2016. *Microbiome* [Internet]. 2019 Dec [cited 2020 May 28];7(1):31. Available from: https://microbiomejournal.biomedcentral.com/articles/10.1186/s40168-019-0620-y

3. Wilkins LJ, Monga M, Miller AW. Defining dysbiosis for a cluster of chronic diseases. *Sci Rep* [Internet]. 2019 Dec 9 [cited 2019 Nov 26];9(1):12918. Available from: http://www.nature.com/articles/s41598-019-49452-y

4. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrovino JF, Costa-Mattioli M. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell* [Internet]. 2016 Jun 16 [cited 2017 Mar 13];165(7):1762 – 75. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0092867416307309

5. Jahansouz C, Staley C, Bernlohr DA, Sadowsky MJ, Khoruts A, Ikramuddin S. Sleeve gastrectomy drives persistent shifts in the gut microbiome. *Surg Obes Relat Dis* [Internet]. 2017 Jan 4 [cited 2017 Mar 13];13(6):916 – 24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28279578

6. Peters BA, Shapiro JA, Church TR, Miller G, Trinh-Shevrin C, Yuen E, et al. A taxonomic signature of obesity in a large study of American adults OPEN. [cited 2019 Sep 17];8(1):1 – 3. Available from: http://www.nature.com/scientificreports/.

7. Dinan TG, Cryan JF. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. *J Physiol* [Internet]. 2017 Jan 15 [cited 2017 Mar 13];595(2):489 – 503. Available from: http://doi.wiley.com/10.1113/JP273106

8. Shivani Ghaisas, Joshua Maher and AK. Gut microbiome in health and disease: linking the microbiome-gut-brain axis and environmental factors in. *Crime Justice Am* [Internet]. 2012 [cited 2020 May 14];417 – 21. Available from: http://www.sciencedirect.com/science/article/pii/B9781437735123000160

9. Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. *Nat Neurosci* [Internet]. 2017 Feb 16 [cited 2017 Mar 13];20(2):145 – 55. Available from: http://www.nature.com/doifinder/10.1038/nn.4476

10. Li Q, Han Y, Dy ABC, Hagerman RJ. The gut microbiota and autism spectrum disorders. *Front Cell Neurosci*. 2017 Apr;11:120.

11. Mayer EA, Knight R, Mazmanian SK, Cryan JF, Tillisch K. Gut microbes and the brain: paradigm shift in neuroscience. *J Neurosci* [Internet]. 2014 Nov 12 [cited 2017 Mar 13];34(46):15490 – 6. Available from: http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.3299-14.2014

12. Kho ZY, Lal SK. The human gut microbiome—a potential controller of wellness and disease. *Front Microbiol* [Internet]. 2018 Aug 14 [cited 2019 Nov 27];9:1835. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30154767

13. Berer K, Krishnamoorthy G. Commensal gut flora and brain autoimmunity: a love or hate affair? *Acta Neuropathol*. 2012;123(5):639 – 51.

14. Kushner RF, Sorensen KW. Lifestyle medicine: the future of chronic disease management. *Curr...
Attaye I, Pinto-Sietsma SJ, Herrema H, Nieuwdorp M. A crucial role for diet in the relationship between gut microbiota and cardiometabolic disease. Annu Rev Med [Internet]. 2019 Sep 3 [cited 2019 Sep 17];71;149–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31479620

Guthrie L, Gupta S, Daily J, Kelly L. Human microbiome signatures of differential colorectal cancer drug metabolism. npj Biofilms Microbiomes [Internet]. 2017 Dec 1 [cited 2019 Feb 14];3(1):27. Available from: http://www.nature.com/articles/s41522-017-0034-1

Kok CR, Hutkins R. Yogurt and other fermented foods in the pursuit of happiness. Neuropharmacol Dis Treat [Internet]. 2015 Mar [cited 2017 Mar 13];11:715–23. Available from: http://www.dovepress.com/psychobiotics-and-the-gut-brain-axis-in-the-pursuit-of-happiness-peer-reviewed-article-NDT

Zhou L, Foster JA. Psychobiotics and the gut-brain axis: in the pursuit of happiness. Neuropharmacol Dis Treat [Internet]. 2015 Mar [cited 2017 Mar 13];11:715–23. Available from: http://www.dovepress.com/psychobiotics-and-the-gut-brain-axis-in-the-pursuit-of-happiness-peer-reviewed-article-NDT

Kok CR, Hutkins R. Yogurt and other fermented foods as sources of health-promoting bacteria. Nutr Rev [Internet]. 2018 Dec 1 [cited 2019 Feb 13];76 (Supplement_1):4–15. Available from: https://academic.oup.com/nutritionreviews/article/76/Supplement_1/4/5185609

Guthrie L, Gupta S, Daily J, Kelly L. Human microbiome signatures of differential colorectal cancer drug metabolism. npj Biofilms Microbiomes [Internet]. 2017 Dec 1 [cited 2019 Feb 14];3(1):27. Available from: http://www.nature.com/articles/s41522-017-0034-1

15. Hartman RE, Patel D. Dietary approaches to the management of autism spectrum disorders. In: Adv Neurobiol. Springer; 2020;24: 547 – 71.

16. Suskind DL, Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn’s disease. Inflamm Bowel Dis [Internet]. 2015 Mar [cited 2018 Nov 8];21(3):556–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25647155

17. Rossen NG, Fuentes S, Van Der Spek MJ, Tijssen JG, Hartman JHA, Duflou A, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. 2015 Jul 1;149(1):110-118.e4

18. Kang D-W, Adams JB, Coleman DM, Pollard EL, Maldonado J, McDonough-Means S, et al. Long-term safety and efficacy of fecal microbiota transplant in active ulcerative colitis. Drug Saf. 2019 Jul 1;42 (7):869 – 80.

19. Hartman RE, Patel D. Dietary approaches to the management of autism spectrum disorders. In: Adv Neurobiol. Springer; 2020;24: 547 – 71.

20. Suskind DL, Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn’s disease. Inflamm Bowel Dis [Internet]. 2015 Mar [cited 2018 Nov 8];21(3):556–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25647155

21. Kang D-W, Adams JB, Coleman DM, Pollard EL, Maldonado J, McDonough-Means S, et al. Long-term safety and efficacy of fecal microbiota transplant in active ulcerative colitis. Drug Saf. 2019 Jul 1;42 (7):869 – 80.

22. Suskind DL, Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn’s disease. Inflamm Bowel Dis [Internet]. 2015 Mar [cited 2018 Nov 8];21(3):556–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25647155

23. Ding X, Li Q, Li P, Zhang T, Cui B, Ji G, et al. Long-term safety and efficacy of fecal microbiota transplant in active ulcerative colitis. Drug Saf. 2019 Jul 1;42 (7):869 – 80.

24. Rossen NG, Fuentes S, Van Der Spek MJ, Tijssen JG, Hartman JHA, Duflou A, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. 2015 Jul 1;149(1):110-118.e4

25. Cueva C, Gil-Sánchez I, Ayuda-Durán B, González-Manzano S, González-Paramás AM, Santos-Buelga C, et al. An integrated view of the effects of wine polyphenols and their relevant metabolites on gut and host health. Molecules [Internet]. 2017 Jan 6 [cited 2019 Nov 26];22(1):99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28067835

26. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poulet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci [Internet]. 2010 Aug 17 [cited 2019 Nov 26];107 (33):14691 – 6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20679230

27. García-Diez J, Alheiro J, Pinto AL, Soares L, Falco V, Fraqueza MJ, et al. Influence of food characteristics and food additives on the antimicrobial effect of garlic and oregano essential oils. Foods (Basel, Switzerland) [Internet]. 2017 Jun 10 [cited 2017 Aug 20];6(6):44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28604598

28. Williams B, Grant L, Gidley M, Mikkelsen D. Gut Fermentation of Dietary Fibres: Physico-chemistry of plant cell walls and implications for health. Int J Mol Sci [Internet]. 2017 Oct 20 [cited 2019 Feb 14];18 (10):2203. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29053599

29. Wang H, Lu Y, Yan Y, Tian S, Zheng D, Leng D, et al. Promising treatment for type 2 diabetes: fecal microbiota transplantation reverses insulin resistance and impaired islets. Front Cell Infect Microbiol. 2020 Jan 17;9:455.

30. Search of: autism | diet - Results on Map - ClinicalTrials.gov [Internet]. [cited 2020 Apr 28]. Available from: https://clinicaltrials.gov/ct2/results?term=autism&cond=diet&map?term=autism&cond=diet&map=

31. Search of: fecal transplant - List Results - ClinicalTrials.gov [Internet]. [cited 2018 Nov 8]. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=fecal+-transplant&ctrid=&state=&city=&dist=&-Search=Search

32. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics. 2011;128(2)344 – 55.

33. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, et al. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006;118(2):511 – 21.

34. Tribe RM, Taylor PD, Kelly NM, Rees D, Sandall J, Kennedy HP. Parturition and the perinatal period: can
mode of delivery impact on the future health of the neonate? J Physiol [Internet]. 2018 Dec 1 [cited 2020 Jul 19];596(23):5709 – 22. Available from: /pmc/articles/PMC6265543/?report=abstract.

35. Axelsson PB, Clausen TD, Petersen AH, Hageman I, Pinborg A, Kessing LV, et al. Relation between infant microbiota and autism: results from a National Cohort Sibling Design Study. *Epidemiology*. 2019 Jan 1;30 (1):52 – 60.

36. Stinson LF, Payne MS, Keelan JA. A critical review of the bacterial baptism hypothesis and the impact of cesarean delivery on the infant microbiome. *Front Med*. 2018.

37. Curran EA, O’Neill SM, Cryan JF, Kenny LC, Dinan TG, Khakan AS, Kearney PM. Research review: Birth by caesarean section and development of autism spectrum disorder and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *J Child Psychol Psychiatry*. 2015 May;56(5):500–8. doi: 10.1111/jcpp.12351. Epub 2014 Oct 27. PMID: 25348074.

38. Curran EA, Khaskan AS, Dalman C, Kenny LC, Cryan JF, Dinan TG, Kearney PM. Obstetric mode of delivery and attention-deficit/hyperactivity disorder: a sibling-matched study. *Int J Epidemiol*. 2016 Apr;45(2):532–42. doi: 10.1093/ije/dyw001. Epub 2016 Apr 10. PMID: 27063604.

39. Seelig MS. Mechanisms by which antibiotics increase the incidence and severity of candidiasis and alter the immunological defenses. *Bacteriol Rev*. 1966;30 (2):442–459.

40. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*. [Internet]. 2013 Dec 19 [cited 2017 Mar 13];155(7):1451 – 63. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0092867413014736

41. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*. [Internet]. 2015 Apr 9 [cited 2019 May 26];161(2):264 – 76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25860609

42. Javurek AB, Spollen WG, Johnson SA, Bivens NJ, Bromert KH, Givan SA, et al. Effects of exposure to bisphenol A and ethinyl estradiol on the gut microbiota of parents and their offspring in a rodent model. *Gut Microbes*. [Internet]. 2016 Nov [cited 2017 Mar 13];7 (6):471 – 85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27624382

43. Krajmalnik-Brown R, Lozupone C, Kang D-W, Adams JB. Gut bacteria in children with autism spectrum disorders: challenges and promise of studying how a complex community influences a complex disease. *Microb Ecol Health Dis*. [Internet]. 2015 [cited 2017 Mar 13];26:26914. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25769266

44. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: A systematic review and meta-analysis. Vol. 8, *Journal of Crohn's and Colitis*. 2014. p. 1569 – 81.

45. Lam WC, Zhao C, Ma WJ, Yao L. The clinical and steroid-free remission of fecal microbiota transplantation to patients with ulcerative colitis: a meta-analysis. 2019 [cited 2020 Jun 24]; Available from: https://doi.org/10.1155/2019/1287493

46. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, et al. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome*. 2017;5(1).

47. Greenhough B, Read CJ, Lorimer J, Lezaun J, McLeod C, Benezra A, et al. Setting the agenda for social science research on the human microbiome. *Palgrave Commun*. [Internet]. 2020 Dec 1 [cited 2020 Jun 25];6(1):1 – 11. Available from: https://www.nature.com/articles/s41599-020-0388-5

48. Gu G, Ottesen A, Bolten S, Luo Y, Rideout S, Nou X. Microbiome convergence following sanitizer treatment and identification of sanitizer resistant species from spinach and lettuce rinse water. *Int J Food Microbiol*. [Internet]. 2020 Apr 2 [cited 2020 Jun 25];318. Available from: https://pubmed.ncbi.nlm.nih.gov/31816526/.

49. Pidot SJ, Gao W, Bouljens AH, Monk IR, Guerillot R, Carter GP, et al. Increasing tolerance of hospital *Enterococcus faecium* to handwash alcohols. *Sci Transl Med*. [Internet]. 2018 Aug 1 [cited 2020 Jun 25];10 (452). Available from: https://stm.sciencemag.org/content/10/452/eaar6115

50. Dietert RR. The microbiome in early life: self-completion and microbiota protection as health priorities. *Birth Defects Res Part B - Dev Reprod Toxicol*. 2014;101(4):333 – 40.

51. York A. Microbiota succession in early life. *Nat Rev*. 2020 [Internet]. 2019 Jun 17 [cited 2020 Jun 25]; Available from: https://www.nature.com/articles/d42859-019-00010-6

52. Black E, Cartwright A, Bakhariba S, Al-Mekaty E, Alsahan D. A qualitative study of pharmacists’ perceptions of, and recommendations for improvement of antibiotic use in Qatar. *Int J Clin Pharm*. [Internet]. 2014 Aug [cited 2020 Jun 4];36(4):787 – 94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24899213

53. Aljayyousi GF, Abdel-Rahman ME, El- Heneidy A, Kurdi R, Faisal E. Public practices on antibiotic use: a cross-
sectional study among Qatar University students and their family members. PLoS One. 2019;14(11).

54. Moienzadeh A, Massoud T, Black E. Evaluation of the general public’s knowledge, views and practices relating to appropriate antibiotic use in Qatar. Int J Pharm Pract. 2017 Apr 1;25(2):133–9.

55. Hamad AF, Alessi-Severini S, Mahmud SM, Brownell M, fan Kuo I. Prenatal antibiotics exposure and the risk of autism spectrum disorders: a population–based cohort study. PLoS One [Internet]. 2019 [cited 2020 Jun 25];14(8). Available from: /pmc/articles/PMC6715235/?report=abstract.

56. Lee E, Cho J, Kim KY. The association between autism spectrum disorder and pre-and postnatal antibiotic exposure in childhood—a systematic review with meta-analysis [Internet]. Vol. 16, Int J Environ Res Public Health. MDPI AG; 2019 [cited 2020 Jun 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/31652518/.

57. Lee E, Cho J, Kim KY. The association between autism spectrum disorder and pre- and postnatal antibiotic exposure in children—a systematic review with meta-analysis [Internet]. Vol. 16, Int J Environ Res Public Health. MDPI AG; 2019 [cited 2020 Jun 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/31652518/.

58. Lee E, Cho J, Kim KY. The association between autism spectrum disorder and pre-and postnatal antibiotic exposure in childhood—a systematic review with meta-analysis [Internet]. Vol. 16, Int J Environ Res Public Health. MDPI AG; 2019 [cited 2020 Jun 25]. Available from: https://pubmed.ncbi.nlm.nih.gov/31652518/.

59. Zhang Y–J, Li S, Man R–Y, Zhou T, Xu D–P, Li H–B. Impacts of gut bacteria on human health and diseases. Int J Mol Sci [Internet]. 2015 Apr 2 [cited 2017 Mar 13];16(4):7493 – 519. Available from: http://www.mdpi.com/1422-0067/16/4/7493/.

60. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med. 2014;20 (2):159 – 66.

61. Chen Z, Guo L, Zhang Y, Walzem RL, Pendergast JS, Printz RL, et al. Incorporation of therapeutically modified bacteria into Gut microbiota inhibits obesity. J Clin Invest. 2014;124(8):3391 – 406.

62. Tandon D, Haque MM, RS, Shaikh S, PS, Dubey AK, et al. A snapshot of gut microbiota of an adult urban population from Western region of India. Arora PK, editor. PLoS One. 2018 Apr;13(4):e0195643.

63. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr. 1995 Jun;125(6):1401 –12.

64. Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. The neuropharmacology of butyrate: the bread and butter of the microbiota–gut–brain axis? Neurochem Int. 2016;99:110 – 32.

65. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Heal Promot. 1997;12(1):38 – 48.

66. Nagpal R, Kumar A, Kumar M, Behare P V, Jain S, Yadav H. Probiotics, their health benefits and applications for developing healthier foods: a review. FEMS Microbiol Lett. 2012 Sep;334(1):1 – 15.

67. Moludi J, Maleki V, Vaghfeh-Mehrabany E, Alizadeh M. Metabolic endotoxemia and cardiovascular disease: A systematic review about potential roles of prebiotics and probiotics. Clin Exp Pharmacol Physiol. 2020 Jan;1440-1681.13250.

68. Akbari V, Hendjiani F. Effects of probiotic supplementation in patients with type 2 diabetes: systematic review and meta-analysis. Nutr Rev. 2016 Dec;74 (12):774 – 84.

69. Keska P, Sivamuruthi BS, Chaiyasut C. Do probiotics improve the health status of individuals with diabetes mellitus? A review on outcomes of clinical trials. Biomed Res Int. 2019 Dec;2019:1 – 11.

70. Lau K, Benitez P, Ardissone A, Wilson TL, Collins EL, Lorca G, et al. Inhibition of type 1 diabetes correlated to a Lactobacillus johnsonii N6.2–mediated Th17 bias. J Immunol. 2011 Mar;186(6):3538 – 46.

71. Mangiola F, Ianiro G, Franceschi F, Fagioli S, Gasbarrini G, Gasbarrini A. Gut microbiota in autism and mood disorders. World J Gastroenterol. 2016;22(1):361.

72. Zhang Y, Kutateladze TG. Diet and the epigenome. Nat Commun. 2018;9(1).

73. Hashemzadeh M, Rahimi A, Zare–Farashbandi F, Alavi–Naeini A, Daei A. Transtheoretical model of health behavioral change: A systematic review [Internet]. Vol. 24, Iranian Journal of Nursing and Midwifery Research. Wolters Kluwer Medknow Publications; 2019 [cited 2020 Jun 25]. p. 83 – 90. Available from: /pmc/articles/PMC6390443/?report=abstract.

74. Antonio J, Quaresma S, Poidinger M, Ohshima Y, Vitte J, Ghanoum MA, et al. The gut microbiome as a major regulator of the gut–skin axis. 2018 [cited 2019 Sep 16]; Available from: www.frontiersin.org

75. Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, et al. The gut – liver axis and the interaction with the microbiome. Nat Rev Gastroenterol Hepatol [Internet]. 2018 [cited 2019 Sep 16]; Available from: https://doi.org/10.1038/.

76. Miranda MCG, Oliveira RP, Torres L, Aguiar SLF, Pinheiro–Rosa N, Lemos L, et al. Frontline science: abnormalities in the gut mucosa of non–obese diabetic mice precede the onset of type 1 diabetes. J Leukoc Biol. 2019;106(3):513 – 29.
77. Salameh M, Burney Z, Mhaimeed N, Laswi I, Yousri NA, Bendriss G, et al. The role of gut microbiota in atopic asthma and allergy, implications in the understanding of disease pathogenesis. Vol. 91, *Scand J Immunol*. Blackwell Publishing Ltd; 2020.

78. Parents Seek Help: Child with Severe Autism Eats Only Sweets | Autism Speaks [Internet]. [cited 2020 Jun 4]. Available from: https://www.autismspeaks.org/expert-opinion/parents-seek-help-child-severe-autism-eats-only-sweets

79. Fernandes AB, Alves da Silva J, Almeida J, Cui G, Gerfen CR, Costa RM, et al. Postingestive modulation of food seeking depends on vagus-mediated dopamine neuron activity. *Neuron*. 2020 Apr;0(0).