

COMMENTARY

Endometriosis and the effects of dietary interventions: what are we looking for?

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Abstract

Endometriosis is the most prevalent benign gynaecologic disease with invalidating effects on the quality of life and decreased economic productivity. As pharmacologic and surgical treatment are only partially effective, women look for self-management strategies in order to control their symptoms. Many dietary interventions have been claimed successful. But it is unclear whether these effects are caused by the idea of taking control of the symptoms by adhering to a diet or by the dietary intervention itself. In order to gain more evidence with regard to the mechanisms behind the effect of dietary intervention in the management of endometriosis, a number of issues need to be addressed for future studies. First, we need clearly defined endpoints in our studies. Secondly, we have to be aware of the difference between the effects of diet on the risk of developing endometriosis and the effects of diet on symptoms in women with already established endometriosis. Thirdly, it may be difficult to strictly define the intervention diet and the control or placebo diet. Fourthly, we have to define endometriosis-related as well as patient-related factors that may influence the success of a dietary intervention. Fifthly, we have to understand the biological mechanisms behind the perceived effects of dietary interventions. These issues will be addressed in this opinion paper.

Lay summary

Endometriosis, defined as the presence of endometrium-like tissue located outside the womb, is a gynaecologic disease that affects many women. They experience severe pain, making it difficult for them to go to school or work. Medication or surgery is often not enough to relieve their pain. Therefore, these women look for ways to suppress their pain by changing their way of life. Changing their diet is an option that is often chosen by women with endometriosis. Many women experience that changing their diet helps to suppress pain symptoms. But it is not clear why changing the diet is effective. Processes in the body could be changed by taking or avoiding specific nutrients, but the effect could also be caused by the empowerment that women experience by adhering to a diet. If we want to learn more about the effect of diet on endometriosis, we have to pay attention to the following issues: first, it is important to exactly define the goal of a new study. Secondly, we have to realize that there is a difference between the study of the effect of diet on the risk of developing endometriosis and the effect of diet on endometriosis that has already developed. Thirdly, we have to realize that it can be difficult to define what the diet contains and how a control group should be defined. Fourthly, it is important to define factors that make it difficult to adhere to a diet. Fifthly, we need to try to understand what happens in the body that may cause the effect of a diet in endometriosis. In this opinion paper, these issues will be addressed.

Keywords: ▶ endometriosis ▶ diet ▶ self-management ▶ empowerment

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Introduction

Endometriosis is the most prevalent benign gynaecologic disease, affecting approximately 5–10% of women of reproductive age. It is described as the presence of functioning endometrium-like tissue outside the uterine cavity. The burden of the disease is high, both regarding the quality of life and from an economic perspective (Della Corte *et al.* 2020). Symptoms include dysmenorrhea, dyspareunia, dyschezia, dysuria, chronic pelvic pain, fatigue and subfertility. To date, the exact pathogenesis and pathophysiology are unknown. Theories regarding the cause of endometriosis are retrograde menstruation, coelomic metaplasia and lymphatic and vascular metastasis. Interaction of proinflammatory, endocrine, immunologic and proangiogenic processes are involved (Zondervan *et al.* 2020).

Medical and surgical treatment options for endometriosis are often not sufficient to alleviate symptoms for women suffering from endometriosis. Medical treatment involves hormonal therapy. This is often only partially effective, has numerous side effects and hampers the option to become pregnant (Zondervan *et al.* 2020). Surgical interventions are associated with invalidating complications including bowel and bladder dysfunction and considerable recurrence of symptoms. Therefore, many women with endometriosis feel the need to develop non-medical tools that they can use to control the symptoms associated with endometriosis themselves. Empowering patients suffering from chronic illnesses including endometriosis, by giving them opportunities to positively influence their symptoms, could decrease feelings of helplessness and increase the quality of life (O'Hara *et al.* 2019). Self-management activities may be important empowering tools. Self-management strategies are defined as skills that are used by an individual to control various aspects of life, including pain and other symptoms of diseases. Women with endometriosis often use different self-management strategies such as self-care, complementary therapies and lifestyle interventions. Among lifestyle interventions are heat, rest, exercise, meditation or dietary changes. In a recent Australian cross-sectional study among 484 women with endometriosis, 76% of them used self-management strategies. Almost half (44%) of them chose a dietary intervention. They reported an effect of their dietary intervention with a score of 6.4 (S.D. 2.4) out of 10 (Armour *et al.* 2019). In our own study among women with endometriosis, more than half of the participants (55.5%) experienced that food influenced their endometriosis-associated symptoms

and that changing their diet alleviated their symptoms (Krabbenborg *et al.* 2021). This may be associated with the fact that many endometriosis patients experience gastrointestinal symptoms.

Diet is a complex entity in relation to its effect on health and disease. A healthy diet is promoted by many governmental institutions. Across the globe, it is defined as a diet which is mostly plant-based and low in animal products. This translates to a diet rich in vegetables, fruit, legumes, nuts, fish, whole grain products, low-fat dairy, low in red meat, alcoholic and sugar-sweetened drinks, salt and saturated fatty acids (Dutch Health Council 2015). It is known that a healthy diet decreases the risk of developing chronic illnesses including hypertension, coronary heart disease and diabetes mellitus type II. However, it is unknown if adhering to a healthy diet will suppress symptoms in women with endometriosis, as it is unknown if these symptoms are related to unhealthy aspects of their diet. Although dietary changes were rated as the third most successful self-management strategies after cannabis and heat, no single diet appeared to provide greater self-reported benefits than others (Armour *et al.* 2019, 2021). This was corroborated by our study in which patients reported that avoiding or limiting a wide range of nutrients including gluten, dairy, soy, sugar and coffee was helpful in alleviating their symptoms as well as adding vegetables, ginger or fruit (Krabbenborg *et al.* 2021). Recently, a large number of papers have been published about the role of nutrition in the management of endometriosis (reviewed by Parazzini *et al.* 2013, Huijs & Nap 2020, Nirgianakis *et al.* 2021). A variety of dietary adjustments have been proposed to suppress endometriosis. However, despite the attention that doctors and patients pay to the role of diet in endometriosis, it is unclear which dietary intervention is most successful and why. How come?

It is obvious that endometriosis is a heterogeneous disease and we have to acknowledge that the clinical studies that have been conducted in the field of endometriosis and diet are heterogeneous, too. If we are to understand the effect of an intervention on a population, it is important to precisely describe the research question, the research population, the exact intervention and its rationale. After having collected and understood evidence in this well-described way, we may be able to generalize principles and apply them to more heterogeneous patient populations. This will also be the basis of understanding the effect of nutrition on endometriosis-associated symptoms. Based on experiences from earlier studies about diet and endometriosis, there are some considerations that should be taken into account in future studies and when

counseling patients about diet. First, we need clearly defined endpoints in our studies. Secondly, we have to be aware of the difference between the effects of diet on the risk of developing endometriosis which are derived from observational studies and the effects of diet on symptoms in women with already established endometriosis measured in intervention studies. Thirdly, it may be difficult to strictly define the intervention diet and the control or placebo diet. Especially when subjective outcomes such as pain, well-being or quality of life are used, placebo effects are likely to play a role and these should be controlled for. Fourthly, we have to define endometriosis-related as well as patient-related factors that may influence the success of a dietary intervention. Fifthly, we have to understand the biological mechanisms behind the perceived effects of dietary interventions. These issues will be addressed in this opinion paper.

What is the endpoint?

In a recent systematic review by our group, we found possible effects on endometriosis-related symptoms by adding vitamin D, polyunsaturated fatty acids, anti-oxidants, removal of gluten and soy, adherence to the FODMAP diet and an anti-inflammatory diet (Huijs & Nap 2020). In these studies, different endpoints were used, including pain (Ailawadi *et al.* 2004, Sesti *et al.* 2007, Indraccolo & Barbieri 2010, Cobellis *et al.* 2011, Giugliano *et al.* 2013, Almassinokiani *et al.* 2016, Morales-Prieto *et al.* 2018, De Leo *et al.* 2019), quality of life (Sesti *et al.* 2007), ASRM score (Ailawadi *et al.* 2004), volume of ovarian endometriosis cyst (De Leo *et al.* 2019), recurrence of ovarian endometriosis cyst after surgery (Sesti *et al.* 2009), bleeding patterns (Morales-Prieto *et al.* 2018), pregnancy (Caserta *et al.* 2014), response to diet (Moore *et al.* 2017) or combinations of these. Pain was measured as VAS score and further specified as chronic pain, dysmenorrhea, dyspareunia and dyschezia or measured in the use of analgesics in different studies. In another recent systematic review, not only comparable endpoints (Nirgianakis *et al.* 2021) but also measures of oxidative stress such as plasma lipid hydroperoxides, malondialdehyde, vitamins and glutathione peroxidase activity were used (Mier-Cabrera *et al.* 2009). In qualitative studies, endpoints may be formulated in a less strictly defined way. In a semi-structured interview study with women with endometriosis, the endpoint of the study was defined as patients' experiences after using a diet. Patients who had changed their diets in various ways reported various subjective effects of the dietary interventions

(Vennberg Karlsson *et al.* 2020). In animal studies, pain is a less suitable endpoint as it is difficult to measure pain in animals (van Aken *et al.* 2020). In these studies, other endpoints have been defined including lesion size or weight, adhesions, angiogenesis, signs of adhesion or invasiveness of endometrial implants and plasma levels of different cytokines (Nirgianakis *et al.* 2021).

In order to report the effects of dietary interventions on endometriosis-associated symptoms, we need to clearly define what the endpoints are. In a clinical setting, pain has frequently been used as an endpoint. However, when we are interested in measuring the effect of a dietary intervention in women with endometriosis, quality of life may be a more relevant endpoint than only pain. A dietary intervention may be a lifelong change, with social and financial consequences. If pain is alleviated after changing the diet but the diet is expensive, not tasteful and difficult to adhere to if not home-cooked, it may not result in a higher quality of life. Another relevant clinical endpoint is fertility. To date, no large, randomized studies have been published on endometriosis patients about the effect of diet on fertility, and therefore, no evidence-based advices can be given about this topic. When talking to patients, this should be stressed to avoid feelings of guilt about not becoming pregnant when failing to adhere to a dietary change for endometriosis.

If we want to unravel the mechanism of the effect of a dietary intervention, it may be useful to use lesion size or lesion weight as an endpoint. However, for the clinical situation, it is known that these are not related to pain. Therefore, they may be less relevant clinical endpoints. Inflammatory markers such as plasma levels of cytokines, interleukins or local inflammation markers may be used to study the biological mechanism by which diet affects endometriosis symptoms. The clinical relevance of these markers may be limited, but these results may be important to increase evidence about the biochemical consequences of dietary interventions.

Preventing endometriosis or suppressing symptoms in established endometriosis?

It is important to notice the difference between the role of diet in the risk of developing endometriosis and a dietary intervention with the aim to suppress endometriosis-related symptoms. Both can be found in the literature. However, associations between intake of nutrients and risk to develop a disease are no proof of a causal effect, and nutrients that influence the risk of developing

endometriosis do not necessarily have the same effect on already established endometriosis.

In a number of large, well-conducted epidemiological studies, a high consumption of vitamin D (Harris *et al.* 2013), a high consumption of fruits and especially citrus fruits (Harris *et al.* 2018), a high consumption of dairy during adolescence (Nodler *et al.* 2020) and a high consumption of long-chain omega 3 fatty acids (Missmer *et al.* 2010) were associated with a lower risk of developing endometriosis. In a population of infertile women, an association was found between intake of caffeinated beverages and endometriosis (Grodstein *et al.* 1993). A high intake of red meat (Yamamoto *et al.* 2018), a high consumption of trans-unsaturated fat (Missmer *et al.* 2010) and alcohol use (Matalliotakis *et al.* 2008) were associated with a higher risk of developing endometriosis. An increased risk of developing endometriosis was also associated with a high intake of cruciferous vegetables (Harris *et al.* 2018) and a high intake of beta carotene and fruits (Trabert *et al.* 2011), however, these results are partly contradictory to other findings (Harris *et al.* 2018).

The effect of these nutrients on symptoms in women with already established endometriosis has not been confirmed for citrus fruit, red meat, alcohol and caffeine. Despite this, in some endometriosis diets, women are given the advice to avoid red meat, caffeine and alcohol. Although this advice is understandable and prudent from a healthy diet point of view, evidence that avoiding these items will suppress endometriosis-related symptoms is lacking. In future studies as well as in future reviews, it should be clearly indicated whether the diet is investigated in relation to the risk to develop endometriosis or in relation to established disease.

How is a dietary intervention defined?

In prospective comparative studies, a well-defined intervention is applied to the intervention group and compared to no intervention or placebo in the control group. In the case of surgery, a surgical intervention is compared to no surgical or sham intervention. In the case of pharmacological treatment, the pharmacological agent that is studied is applied to the intervention group and no agent or placebo is applied to the control group. It is much more complex to compare a dietary intervention with no dietary intervention. Diet is not fixed, but a variable in everyday life. It may change in time with taste, season, budget and social factors. Moreover, dietary interventions – especially when multiple foods and drinks are involved – are

difficult or impossible to blind for. Finding an appropriate placebo diet that is similar in taste, energy content and ease of use is another problem, while having such a placebo diet is crucial in studies that rely on symptom data (Moayyedi *et al.* 2020). In some studies, this problem has been addressed by applying fixed amounts in the form of supplements of vitamins, mineral salts, lactic ferments and/or fatty acids (Ailawadi *et al.* 2004, Mier-Cabrera *et al.* 2009, Indraccolo & Barbieri 2010, Cobellis *et al.* 2011, Giugliano *et al.* 2013, Almassinokiani *et al.* 2016, Signorile *et al.* 2018, De Leo *et al.* 2019). In a number of studies, amounts were individually assigned to patients according to their BMI, physical activity and job (Sesti *et al.* 2007, 2009). Although supplements may help to standardize the intervention, they also may add to the feeling of medicalization of the diet, especially if these items are provided in tablets or drops. This may be a negative factor for adherence. Moreover, foods rich in certain nutrients, for example, fish as a source of omega-3 fatty acids or vegetables as a source of antioxidant vitamins, provide other potentially beneficial nutrients, minerals, vitamins, or dietary fibers, which make them more desirable than supplements. In other studies, less well-defined dietary interventions were applied including the Mediterranean diet (Ott *et al.* 2012), the low-FODMAP diet (Moore *et al.* 2017) and a gluten-free diet (Marziali *et al.* 2012, Caserta *et al.* 2014). A diet in which the interventions are less strictly defined may be more easier to adhere to as it adds to the feeling of empowerment for patients themselves and avoids feelings of medicalization. On the other hand, it can be difficult for participants to adhere to the diet because it may be unclear which foods or nutrients are allowed to take. Interpretation of the results of a study with a less strictly defined intervention may also be more difficult, although diet scores that reflect adherence to the dietary guidelines such as the MedDiet score in the Food4Me study (Livingstone *et al.* 2016) are helpful. Therefore, the diet should be as exactly described as possible. Patients should be taught about the rationale of the diet, about the nutrients that fit in and the nutrients that should be avoided. In the study by Moore and coworkers, a nurse-specialist who was trained by an experienced dietician instructed participants in a one-on-one session on how to apply the low-FODMAP diet. Moreover, the low-FODMAP digital app and booklet were provided (Moore *et al.* 2017). This is not only important to support women who are participating in the study, but it is also necessary to make the intervention as standardized as possible thereby stimulating reliable outcomes. Future studies should address and measure adherence to their diet so any lack of effect might be explained by non-use or

non-compliance and associations between adherence and study outcomes can be done (Young *et al.* 2019).

Which dietary intervention for which patient?

Endometriosis-related factors as well as individual patient factors will influence whether a dietary intervention is effective. To date, the majority of studies on endometriosis patients have focused on the effect of a dietary intervention on pain. Studies about the effect of diet on fertility are scarce. In one case report, pregnancy occurred in a woman with ovarian endometriosis 3 months after cessation of soy (Chandrareddy *et al.* 2008) and in another, pregnancy was reported after initializing a gluten-free diet in a woman with an ovarian cyst (Caserta *et al.* 2014). Studies about the effect of vitamin D on endometriosis-associated symptoms are conflicting (Ailawadi *et al.* 2004, Almassinokiani *et al.* 2016), and in studies about the effect of vitamin D on fertility in women with endometriosis no clear conclusions could be drawn (Voulgaris *et al.* 2017, Chen & Zhi 2020). Evidence is lacking about other nutritional factors and their effects on endometriosis-related subfertility. To date, no evidence-based advice can be given to women with endometriosis and subfertility concerning effective dietary interventions. With regard to the effect of dietary interventions on ovarian endometrioma, no difference in recurrence rate was found 18 months after surgery in women with and without a 6-month intervention with supplements containing vitamins, minerals, lactic ferments and fish oil (Sesti *et al.* 2009). In another study, no effect on ovarian cyst size was reported after a 3-month dietary intervention with alpha-lipoic acid, palmitoethanolamide and myrrh, whereas this intervention did have an effect on chronic pelvic pain, dysmenorrhea and dyspareunia (De Leo *et al.* 2019). Therefore, evidence is lacking that dietary interventions may be effective for ovarian endometrioma size and recurrence risk. So different endometriosis-related symptoms such as pain, subfertility or the presence of ovarian endometrioma may determine the kind of dietary advice that can be given and also the strength of the advice, based on the available evidence with regard to the different factors.

Not only endometriosis-related factors but also patient-related factors may determine what dietary intervention may be helpful for women with endometriosis. In patients with irritable bowel syndrome (IBS), a low-FODMAP diet has been proven effective for abdominal pain and abdominal bloating or distension (Black *et al.* 2021).

Therefore, in women with endometriosis and concurrent IBS, a low-FODMAP diet should be considered first, before other dietary interventions (Moore *et al.* 2017). The same holds true for patients with endometriosis and celiac disease. Avoiding gluten is a very effective and safe treatment for celiac disease (Bascunan *et al.* 2017). However, it is difficult to adhere to a lifelong gluten-free diet. In some patients, reintroduction of gluten may be suitable over time (Itzlinger *et al.* 2018). There may be a link between celiac disease and endometriosis since oxidative stress, immunological and inflammatory aspects are supposed to play a role in both illnesses (Santoro *et al.* 2014). In patients with endometriosis also suffering from celiac disease, a gluten-free diet is recommended as the dietary intervention of choice until other dietary advice will be available for patients with celiac disease (Caserta *et al.* 2014).

Finally, individual person-related factors including the quality of the current diet, a patient's sense of urgency to use self-management tools and the motivation and capacity to adhere to a lifelong change in diet will determine the success of a dietary intervention. Careful counseling, based on endometriosis-related factors, patient-related factors and individual person-related factors are indicated in decision-making about dietary interventions.

What is the mechanism?

Many women perceive improvement in endometriosis-related symptoms after a dietary intervention. In a qualitative study, women with endometriosis were asked about their experiences after changing their diet. They reported to have developed awareness of their bodies' reactions, confidence in their bodies, decreased pain, a reduced feeling of illness and energy to live a normal life. In this study, women reported that experiencing intense and disabling pain could be described as 'taking away their life'. The authors hypothesize that by changing their diet, the feeling to be able to take back control and thereby regain quality of life may be responsible for the experienced positive effects of dietary changes, despite the wide variety of the changes (Vennberg Karlsson *et al.* 2020). This again emphasizes the need for a placebo group in diet studies.

Endometriosis is a multifactorial disease. After having assessed the literature on diet and endometriosis risk in 2013, Parazzini concluded that different nutrients may exert different effects on the different stages of disease development (Parazzini *et al.* 2013) and this may well be true. However, some patterns may be recognized in the mechanisms of effect. Inflammation is one of the

main factors in endometriosis. Immune cells involved in the inflammatory response are cytokines, neutrophils, granulocytes (including mast cells and macrophages), chemokines and different subsets of T-cells (Jiang *et al.* 2016). Antioxidants balance oxidative stress, which is present in chronic inflammatory processes. Therefore nutrients with anti-inflammatory characteristics may suppress endometriosis-related pain symptoms. Endometriosis is also an oestrogen dependent disease.

Pharmacological therapy aimed at suppressing oestrogen activity has been proven effective in suppressing pain symptoms (Dunselman *et al.* 2014). Therefore, nutrients with an anti-oestrogen activity may have pain-alleviating properties for women with endometriosis. To increase the evidence about mechanisms of action of dietary interventions, objective effects on pain and quality of life should be investigated together with biochemical markers including cellular, metabolic and (epi-)genetic effects.

Table 1 Methodological recommendations.

Study type	Target population	Dietary intake or intervention	Endpoint
Risk of endometriosis Observational; cross-sectional or cohort study	Girls and women before menopause	Habitual intake assessed by FFQ (nutrients, foods)	Presence (cross-sectional) or new cases (cohort) of endometriosis based on complaints (questionnaires: EHP-30) and clinical confirmation by ultrasound, MRI or surgery
Associations between severity of subjective and clinical endometriosis complaints and diet Cross-sectional study, observational or longitudinal study	Women with clinically confirmed endometriosis	Habitual intake of foods or nutrients by FFQ	Subjective outcomes: pelvic pain, mood and quality of life Clinical outcomes: subfertility; presence of endometriosis lesions on ultrasound, MRI or surgery and cyst size
Effect of diet on endometriosis-related complaints Intervention, one group design with measurements before and after start of diet	Women with clinically confirmed endometriosis; subgroups based on type of endometriosis; use of oral contraceptives; past surgical treatment for endometriosis	Whole diet: (e.g. Mediterranean, healthy eating); Elimination diet: (e.g. low FODMAP); specific foods: (e.g. fruits and vegetables)	Subjective outcomes (e.g. pelvic pain, mood, quality of life) as assessed by questionnaires (EHP-30). Clinical outcomes (e.g. Inflammation markers, presence of endometriosis lesions on ultrasound, MRI or surgery; cyst size)
Intervention, parallel groups including placebo	Women with clinically confirmed endometriosis; subgroups based on type of endometriosis; use of oral contraceptives; past surgical treatment for endometriosis	Specific nutrients: (e.g. vitamin D or omega-6 fatty acids)	Subjective outcomes (e.g. pelvic pain, mood, quality of life) as assessed by questionnaires (EHP-30). Clinical outcomes (e.g. Inflammation markers, presence of endometriosis lesions on ultrasound, MRI or surgery, cyst size)
Mechanistic studies Observational or intervention study	Women with clinically confirmed endometriosis	Any dietary intervention	Immune cells in peripheral blood and/or menstrual effluent: cytokines, neutrophils, granulocytes (including mast cells and macrophages), chemokines and different subsets of T-cells

Conclusion

Dietary interventions are promising in the treatment of endometriosis-related symptoms. Different studies have proven that a diet is an empowerment tool for women struggling with endometriosis. Many women with endometriosis are using various dietary interventions to control their pain symptoms and they perceive positive effects, independent of the dietary change itself (Armour *et al.* 2019, 2021, Vennberg Karlsson *et al.* 2020, Krabbenborg *et al.* 2021). This positive effect of adjusting the diet should be stressed when counseling women about the role of diet in endometriosis.

However, evidence is lacking about important aspects of selecting a dietary intervention as part of the treatment plan in endometriosis. To date, it is unknown which dietary intervention has which effect on women with specific types of endometriosis or specific individual characteristics. Moreover, knowledge about biochemical mechanisms behind the perceived effect is scarce. Evidence points towards pain-relieving effects of a diet with anti-inflammatory and anti-oestrogen characteristics in women with different subtypes of endometriosis and of symptom-suppressing effects of a low-FODMAP or gluten-free diet in women with endometriosis and co-existing IBS or celiac disease (Nirgianakis *et al.* 2021).

To be able to predict which women will benefit most from a dietary intervention, clear endpoints should be defined in future studies (Table 1). Clinical endpoints in relation to fertility could be the live birth rate. A clinical endpoint related to effectiveness in relation to the suppression of symptoms could be quality of life rather than pain. A dietary intervention is a lifelong change of habits. Therefore, when evaluating the effect of dietary interventions on endometriosis-related symptoms, the consequences of these large changes should be taken into account. Quality of life includes pain as well as diet-related aspects such as tastiness, cost and possibilities to adhere to the diet. As a biochemical endpoint, serum inflammatory markers before and during the dietary intervention could be assessed, or measurement of metabolic markers (Table 1). This could help to unravel the mechanism underlying the perceived effects.

If a dietary change is undertaken, it is important to characterize the intervention exactly. In personalized medicine, the necessary amount of nutrients will vary from person to person. Moreover, the dietary intervention will be more drastic for women who had a low-quality diet before starting the intervention than for women who already had a healthy eating pattern. It is important to educate

women about the aim and rationale of the intervention and to instruct them about nutrients that are allowed and which should be avoided. This will help to standardize the intervention, making the results more reliable. In order to increase the reliability of study outcomes, including a control group with a properly defined placebo diet should be considered.

In conclusion, dietary interventions are a powerful self-management tool for women with endometriosis. Future studies with clearly defined endpoints and exactly described characteristics of the diet for well-characterized women with endometriosis will help to design the best individual diet for each individual patient.

Declaration of interest

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Author contribution statement

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References

- Ailawadi RK, Jobanputra S, Kataria M, Gurates B & Bulun SE 2004 Treatment of endometriosis and chronic pelvic pain with letrozole and norethindrone acetate: a pilot study. *Fertility and Sterility* **81** 290–296. (<https://doi.org/10.1016/j.fertnstert.2003.09.029>)
- Almassinokiani F, Khodaverdi S, Solaymani-Dodaran M, Akbari P & Pazouki A 2016 Effects of vitamin D on endometriosis-related pain: a double-blind clinical trial. *Medical Science Monitor* **22** 4960–4966. (<https://doi.org/10.12659/msm.901838>)
- Armour M, Sinclair J, Chalmers KJ & Smith CA 2019 Self-management strategies amongst Australian women with endometriosis: a national online survey. *BMC Complementary and Alternative Medicine* **19** 17. (<https://doi.org/10.1186/s12906-019-2431-x>)
- Armour M, Middleton A, Lim S, Sinclair J, Varjabedian B & Smith CA 2021 Dietary practices of women with endometriosis: a cross-sectional survey. *Journal of Alternative and Complimentary Medicine* **27** 771–777. (<https://doi.org/10.1089/acm.2021.0068>)
- Bascunan KA, Catalina Vespa MC & Araya M 2017 Celiac disease: understanding the gluten free diet. *European Journal of Nutrition* **56** 449–459. (<https://doi.org/10.1007/s00394-016-1238-5>)
- Black CJ, Staudauer HM & Ford AC 2021 Efficacy of a low FODMAP diet in irritable bowel syndrome: systematic review and network meta-analysis. *Gut* **71** 1117–1126. (<https://doi.org/10.1136/gutjnl-2021-325214>)

- Caserta D, Matteucci E, Ralli E, Bordi G & Moscarini M** 2014 Celiac disease and endometriosis: an insidious and worrisome association hard to diagnose: a case report. *Clinical and Experimental Obstetrics and Gynecology* **41** 346–348. (<https://doi.org/10.12891/ceog16842014>)
- Chandrareddy A, Muneyirci-Delale O, McFarlane SI & Murad OM** 2008 Adverse effects of phytoestrogens on reproductive health: a report of three cases. *Complementary Therapies in Clinical Practice* **14** 132–135. (<https://doi.org/10.1016/j.ctcp.2008.01.002>)
- Chen Y & Zhi X** 2020 Roles of vitamin D in reproductive systems and assisted reproductive technology. *Endocrinology* **161** bqaa023. (<https://doi.org/10.1210/endo/bqaa023>)
- Cobellis L, Castaldi MA, Giordano V, Trabucco E, De Franciscis P, Torella M & Colacurci N** 2011 Effectiveness of the association micronized N-palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **158** 82–86. (<https://doi.org/10.1016/j.ejogrb.2011.04.011>)
- De Leo V, Cagnacci A, Cappelli V, Biasioli A, Leonardi D & Seracchioli R** 2019 Role of a natural integrator based on lipoic acid, palmitoylethanolamide and myrrh in the treatment of chronic pelvic pain and endometriosis. *Minerva Ginecologica* **71** 191–195. (<https://doi.org/10.23736/S0026-4784.19.04384-3>)
- Della Corte LH, DiFilippo C, Gabrielli O, Reppuccia S, LaRosa VL, Ragusa R, Fichera M, Commodari E, Bifulco G & Giampaolino P** 2020 The Burden of endometriosis on women's lifespan: a narrative overview on quality of life and psychosocial wellbeing. *International Journal of Environmental Research and Public Health* **17** 4683. (<https://doi.org/10.3390/ijerph17134683>)
- Dunselman GAJ, Vermeulen N, Becker CM, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap AW, et al.** 2014 ESHRE Guideline: management of women with endometriosis. *Human Reproduction* **29** 400–412. (<https://doi.org/10.1093/humrep/det457>)
- Dutch Health Council (Gezondheidsraad) 2015 Richtlijnen goede voeding. (available at: <https://www.gezondheidsraad.nl/documenten/adviezen/2015/11/04/richtlijnen-goede-voeding-2015>). Accessed on 18 November 2021.
- Giughiano E, Cagnazzo E, Soave I, Lo Monte G, Wenger JM & Marci R** 2013 The adjuvant use of N-palmitoylethanolamine and transpolydatin in the treatment of endometriotic pain. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **168** 209–213. (<https://doi.org/10.1016/j.ejogrb.2013.01.009>)
- Grodstein F, Goldman MB, Ryan L & Cramer DW** 1993 Relation of female infertility to consumption of caffeinated beverages. *American Journal of Epidemiology* **137** 1353–1360. (<https://doi.org/10.1093/oxfordjournals.aje.a116644>)
- Harris HR, Chavarro JE, Malspeis S, Willett WC & Missmer SA** 2013 Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. *American Journal of Epidemiology* **177** 420–430. (<https://doi.org/10.1093/aje/kws247>)
- Harris HR, Eke AC, Chavarro JE & Missmer SA** 2018 Fruit and vegetable consumption and risk of endometriosis. *Human Reproduction* **33** 715–727. (<https://doi.org/10.1093/humrep/dey014>)
- Huijs E & Nap AW** 2020 The effects of nutrients on symptoms in women with endometriosis: a systematic review. *Reproductive Biomedicine Online* **41** 317–328. (<https://doi.org/10.1016/j.rbmo.2020.04.014>)
- Indraco U & Barbieri F** 2010 Effect of palmitoylethanolamide-polydatin combination on chronic pelvic pain associated with endometriosis: preliminary observations. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **150** 76–79. (<https://doi.org/10.1016/j.ejogrb.2010.01.008>)
- Itzlinger A, Branchi F, Elli L & Schumann M** 2018 Gluten-free diet in celiac disease – forever and for all? *Nutrients* **10** 1796. (<https://doi.org/10.3390/nu10111796>)
- Jiang L, Yan Y, Liu Z & Wang Y** 2016 Inflammation and endometriosis. *Frontiers in Bioscience* **21** 941–948. (<https://doi.org/10.2741/4431>)
- Krabbenborg I, De Roos N, Van der Grinten P & Nap A** 2021 Diet quality and perceived effects of dietary changes in Dutch endometriosis patients: an observational study. *Reproductive Biomedicine Online* **43** 952–961. (<https://doi.org/10.1016/j.rbmo.2021.07.011>)
- Livingstone KM, Celis-Morales C, Navas-Carretero S, San-Cristobal R, Macready AL, Fallaize R, Forster H, Woolhead C, O'Donovan CB, Marsaux CFM, et al.** 2016 Effect of an Internet-based, personalized nutrition randomized trial on dietary changes associated with the Mediterranean diet: the Food4Me Study. *American Journal of Clinical Nutrition* **104** 288–297. (<https://doi.org/10.3945/ajcn.115.129049>)
- Marziali M, Venza M, Lazzaro S, Lazzaro A, Micossi C & Stolfi VM** 2012 Gluten-free diet: a new strategy for management of painful endometriosis related symptoms? *Minerva Chirurgica* **67** 499–504.
- Matalliotakis IM, Cakmak H, Fragouli YG, Goumenou AG, Mahutte NG & Arici A** 2008 Epidemiological characteristics in women with and without endometriosis in the Yale series. *Archives of Gynecology and Obstetrics* **277** 389–393. (<https://doi.org/10.1007/s00404-007-0479-1>)
- Mier-Cabrera J, Aburto-Soto T, Burrola-Méndez S, Jiménez-Zamudio L, Tolentino MC, Casanueva E & Hernández-Guerrero C** 2009 Women with endometriosis improved their peripheral antioxidant markers after the application of a high antioxidant diet. *Reproductive Biology and Endocrinology* **7** 54. (<https://doi.org/10.1186/1477-7827-7-54>)
- Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, Barbieri RL, Willett WC & Hankinson SE** 2010 A prospective study of dietary fat consumption and endometriosis risk. *Human Reproduction* **25** 1528–1535. (<https://doi.org/10.1093/humrep/deq044>)
- Moayyedi P, Simren M & Bercik P** 2020 Evidence-based and mechanistic insights into exclusion diets for IBS. *Nature Reviews: Gastroenterology and Hepatology* **17** 406–413. (<https://doi.org/10.1038/s41575-020-0270-3>)
- Moore JS, Gibson PR, Perry RE & Burgell RE** 2017 Endometriosis in patients with irritable bowel syndrome: specific symptomatic and demographic profile, and response to the low FODMAP diet. *Australian and New Zealand Journal of Obstetrics and Gynaecology* **57** 201–205. (<https://doi.org/10.1111/ajo.12594>)
- Morales-Prieto DM, Herrmann J, Osterwald H, Kochhar PS, Schlessner E, Markert UR & Oettel M** 2018 Comparison of dienogest effects upon 3,3'-diindolylmethane supplementation in models of endometriosis and clinical cases. *Reproductive Biology* **18** 252–258. (<https://doi.org/10.1016/j.repbio.2018.07.002>)
- Nirgianakis K, Egger K, Kalaitzopoulos DR, Lanz S, Bally L & Mueller MD** 2021 Effectiveness of dietary interventions in the treatment of endometriosis: a systematic review. *Reproductive Sciences* **24** 1–17. (<https://doi.org/10.1007/s43032-020-00418-w>)
- Nodler JL, Harris HR, Chavarro JE, Frazier AL & Missmer SA** 2020 Dairy consumption during adolescence and endometriosis risk. *American Journal of Obstetrics and Gynecology* **222** 257.e1–257.e16. (<https://doi.org/10.1016/j.ajog.2019.09.010>)
- O'Hara R, Rowe H & Fisher J** 2019 Self-management in condition-specific health: a systematic review of the evidence among women diagnosed with endometriosis. *BMC Women's Health* **19** 80. (<https://doi.org/10.1186/s12905-019-0774-6>)
- Ott J, Nouri K, Hrebacka D, Gutschelhofer S, Huber J & Wenzl R** 2012 Endometriosis and nutrition – recommending a Mediterranean diet decreases endometriosis-associated pain: an experimental observational study. *Journal of Aging Research and Clinical Practice* **1** 162–166.
- Parazzini F, Vigano P, Candiani M & Fedele L** 2013 Diet and endometriosis risk: a literature review. *Reproductive Biomedicine Online* **26** 323–336. (<https://doi.org/10.1016/j.rbmo.2012.12.011>)

- Santoro L, Campo S, D'Onofrio F, Gallo A, Covino M, Campo V, Palombini G, Santoliquido A, Gasbarrini G & Montalto M** 2014 Looking for celiac disease in Italian women with endometriosis: a case control study. *Biomedical Research International* **2014** 236821. (<https://doi.org/10.1155/2014/236821>)
- Sesti F, Pietropoli A, Capozzolo T, Broccoli P, Pierangeli S, Bollea MR & Piccione E** 2007 Hormonal suppression treatment or dietary therapy versus placebo in the control of painful symptoms after conservative surgery for endometriosis stage III–IV. A randomized comparative trial. *Fertility and Sterility* **88** 1541–1547. (<https://doi.org/10.1016/j.fertnstert.2007.01.053>)
- Sesti F, Capozzolo T, Pietropoli A, Marziali M, Bollea MR & Piccione E** 2009 Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **147** 72–77. (<https://doi.org/10.1016/j.ejogrb.2009.07.003>)
- Signorile PG, Viceconte R & Baldi A** 2018 Novel dietary supplement association reduces symptoms in endometriosis patients. *Journal of Cellular Physiology* **233** 5920–5925. (<https://doi.org/10.1002/jcp.26401>)
- Trabert B, Peters U, De Roos AJ, Scholes D & Holt VL** 2011 Diet and risk of endometriosis in a population-based case-control study. *British Journal of Nutrition* **105** 459–467. (<https://doi.org/10.1017/S0007114510003661>)
- van Aken MA, Groothuis PG, Panagiotou M, Duin MV, Nap AW, van Rijn TC, Kozicz T, Braat DD & Peeters AB** 2020 An objective and automated method for evaluating abdominal hyperalgesia in a rat model for endometriosis. *Laboratory Animals* **54** 365–372. (<https://doi.org/10.1177/0023677219856915>)
- Vennberg Karlsson J, Patel H & Premberg A** 2020 Experiences of health after dietary changes in endometriosis: a qualitative study. *British Medical Journal Open* **10** 1–8.
- Voulgaris N, Papanastasiou L, Piaditis G, Angelousi A, Kaltsas G, Mastorakos G & Kassi E** 2017 Vitamin D and aspects of female fertility. *Hormones* **16** 5–21. (<https://doi.org/10.14310/horm.2002.1715>)
- Yamamoto A, Harris HR, Vitonis AF, Chavarro JE & Missmer SA** 2018 A prospective cohort study of meat and fish consumption and endometriosis risk. *American Journal of Obstetrics and Gynecology* **219** 178.e1–178.e10. (<https://doi.org/10.1016/j.ajog.2018.05.034>)
- Young C, Campolonghi S, Ponsonby S, Dawson SL, O'Neil A, Kay-Lambkin F, McNaughton SA, Berk M & Jacka FN** 2019 Supporting engagement, adherence, and behavior change in online dietary interventions. *Journal of Nutrition Education and Behavior* **51** 719–739. (<https://doi.org/10.1016/j.jneb.2019.03.006>)
- Zondervan KT, Becker CM & Missmer SA** 2020 Endometriosis. *New England Journal of Medicine* **382** 1244–1256. (<https://doi.org/10.1056/NEJMra1810764>)

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