COMMENTARY

Sertility

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 crosssectional 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 selfreported 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 welldescribed 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



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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 endometriosisrelated 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 oneon-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



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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 sov (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 evidencebased advice can be given to women with endometriosis and subfertility concerning effective dietary interventions. With regard to the effect of dietary interventions on ovarian endometriomata, 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 patientrelated 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 advises 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 endometriosisrelated 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



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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.

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

Table 1 Methodological recommendations.

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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 antiinflammatory and anti-oestrogen characteristics in women with different subtypes of endometriosis and of symptomsuppressing 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 endometriosisrelated 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 Selfmanagement 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)



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. 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, Muneyyirci-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/endocr/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, palmitoiletanolamide 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/adv iezen/2015/11/04/richtlijnen-goede-voeding-2015). Accessed on 18 November 2021.

Giugliano 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)

Indraccolo U & Barbieri F 2010 Effect of palmitoylethanolamidepolydatin 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)

© 2022 The authors Published by Bioscientifica Ltd 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 Internetbased, 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, Schleussner E, Markert UR & Oettel M 2018 Comparison of dienogest effects upon 3,3'-diindolylmethane supplementation in models of endometriosis and clinical cases. *Reproductive Biolology* **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 conditionspecific 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)



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- 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 woemn with endometriosis: a case control study. *Biomedical Research International* 2014 236821. (https://doi.org/10.1155/2014/236821)
- Sesti F, Pietropolli 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, Pietropolli 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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