

The Female Gut Health Guide Lessons Through Life



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About this resource



This resource is intended for healthcare professionals and describes the bi-directional relationship between gut health and female health*. An overview of the main female sex hormones is provided before their interaction with the gut microbiome is explained, focusing on key life stages including pre-menopause, pregnancy, perimenopause and menopause.

*In this context of this resource, reference to female and/or women's health is referring to the biology of bodies assigned female at birth (AFAB).

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KEY POINTS

- A **bi-directional relationship** exists between the gut microbiome and female sex hormones.
- Sex hormones fluctuate throughout a women's life especially during the **menstrual cycle**, **pregnancy**, **perimenopause** and **menopause**.
- The 'oestrobolome' is a **unique collection of microbes within the gut microbiome** which can recycle oestrogen to reduce its excretion.
- Changes in **gastrointestinal symptoms** throughout the menstrual cycle (e.g., diarrhoea, bloating, constipation) is owed to fluctuating oestrogen and progesterone levels.
- Lower gut microbiota **diversity and dysbiosis** (i.e., an imbalance) are common features of polycystic ovary syndrome (PCOS) and endometriosis.
- The composition and diversity of the gut microbiome has been shown to differ between **healthy and complicated pregnancies**. Additionally, postpartum depression has been linked with the gut-brain axis.
- Postmenopausal women have lower gut microbiome diversity and altered overall composition compared to premenopausal women as well as a **decreased abundance of gut microbial beta-glucuronidase**, the enzyme involved with the oestrobolome.
- **Diet and lifestyle choices** can support female health throughout life by supporting the gut microbiota.

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The Gut Microbiota

The gut microbiota is the collection of microbes (e.g., bacteria, archaea, fungi and viruses) living throughout the gastrointestinal tract. Everyone has a unique gut microbiota.



Battle of the sexes

Differences exist between the male and female gut microbiota.¹¹² These sex-related differences in the gut microbiota, and how they interact with sex hormones and the immune system, is referred to as 'microgenderome'.³ This may, in part, explain why the risk of certain diseases is higher in females compared to men (e.g. autoimmune disease, osteoporosis and irritable bowel syndrome), and vice versa. Considerably greater gut microbiota diversity is seen in females (at bacterial phyla, genus and species level).⁴⁻⁶ However, these differences between sexes lessen throughout life, especially during perimenopause and menopause due to changes in sex hormones.

Mind the Gap

Historically, females have been underrepresented in scientific research owing to biological and physiological differences between sexes. This gender gap persists because including female participants in studies can present challenges, such as accounting for variability stemming from hormonal cycle fluctuations. However, attitudes are shifting, and more research is emerging surrounding women's health in general and in relation to the female gut microbiome.



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The Female Gut Microbiota

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This flowchat describes how the female gut microbiota composition changes throughout life.

Mode of delivery 🥄 🍟 Pregnancy The maternal gut microbiota shapes the Babies born by vaginal delivery are exposed to neonatal gut microbiota, via direct transfer of diverse maternal microbes⁸ and have been shown bacteria.⁷ This process plays a vital role in to have increased bifidobacteria. This is infant development, and can contribute to the associated with a lower risk of childhood neurodevelopment of the infant with infections, atopic disorders, and obesity.9-10 potentially long-term and multi-generational outcomes.7 Childhood Adolescence/Adulthood numbers of *Bifidobacterium* Greater and The gut microbiota composition is determined Bacteroides and lower numbers of Streptococcus by modifiable diet and lifestyle factors. Too and Enterococcus are seen in breastfed babies little exercise, disrupted sleep, heightened compared to those consuming formula milk.¹¹ stress levels and a lack of plant diversity and Additionally, excessive antibiotic usage and/or fibre in the diet can all negatively impact the gut microbiota composition.14-17 increased hygiene measures are associated with reduced gut microbiota diversity during childhood.12-13 Menopause Fertility Recent research has shown a correlation The gut microbiota becomes less diverse, between alterations in gut microbiota reflecting that of the male gut microbiota.²¹ composition and infertility.18-19 Causal Menopause is also associated with lower relationships between the gut microbiota and oestrobolome potential (see page 4).²² female infertility are now being identified,²⁰ however, sufficient evidence to support this causal relationship is still needed. Older adulthood Gut microbiota diversity generally declines with age.²³ Environment: The gut microbiota is Up to ~3 years is the critical window influenced by those you live with of opportunity to modulate the gut (including pet ownership) and those in microbiota composition with greatest the same household will have a more intra- and inter-variability. After this similar microbiota.^{24_25} Exposures such age, the microbiota is more **stable** and as pollution and pathogens will also mature (40%-60% similarity with the adult microbiota).29-31 affect gut microbiota.²⁶⁻²⁸ Find out more at <u>yakult.co.uk/HCP</u> O <u>@yakultscience_ukie</u>

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Female Hormones

Female Sex Hormones



The Oestrobolome

The 'oestrobolome' is a **unique collection of microbes within the gut microbiome** which are capable of **metabolising and regulating circulating oestrogen levels**. Oestrogen circulates the body and is inactivated in the liver before moving to the intestines for excretion in stools.



The oestrobolome essentially **'recycles'** oestrogen by enabling it to re-enter circulation and increase the amount reabsorbed. This reactivation of oestrogen is achieved via excretion of the **beta-glucuronidase enzyme** which is produced by certain types of bacteria in the gut e.g. *Bacteroides* and *Firmicutes*. Therefore, the **composition and diversity of the gut microbiome can impact oestrogen levels** in the body which can subsequently impact various bodily functions, beyond reproductive health. This is because oestrogen plays a role in **weight management**³², supporting **libido**³³, **mood**³⁴, **bone**³⁵, **brain**³⁶, **immune**³⁷ and **heart health**.³⁸

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Menstruation

The gut microbiome plays a role in the menstrual cycle, and vice versa. Menstruation cycles can **vary between women**; however, on average, it lasts **28 days** and includes **3 main phases**:

Follicular phase

Ovulation

Luteal phase

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Oestrogen peaks about midway through the cycle, which causes an increase in the luteinising hormone, triggering ovulation. Progesterone levels then rise to support a fertilised egg. In the absence of pregnancy following ovulation, progesterone and oestrogen levels decline and then menstruation begins (see Figure 1).

Sex hormone fluctuations can also be associated with **menstrual pain sensitivity and symptoms**. Changes in the gut microbiome throughout the menstruation cycle may be associated with premenstrual syndrome (PMS);³⁹ however, more research is needed in this area.

If the gut microbiome is **imbalanced**, this may lead to an imbalance in sex hormones. Cyclical changes in the gut microbiome can impact oestrogen levels as gut health and microbial diversity can influence excretion and recirculation of oestrogen.⁴⁰



Figure 1. Hormonal fluctuation during a normal menstrual cycle.⁴¹

Chidi-Ogbolu & Baar (2019) Front Physiol, 9: 1834.

LH: Luteinizing hormone FSH: Follicle-stimulating hormone



Sex hormones (oestrogen and progesterone) may modulate and influence irritable bowel syndrome (IBS). Approximately 5-20% of the population struggle with IBS,⁴² and women are more likely to suffer than men.^{43–46} Correlations exist between worsened IBS gastrointestinal symptoms and phases of the menstrual cycle, possibly due to elevated prostaglandin levels during menstruation,⁴⁷ highlighting the potential role of sex hormones in this condition.

IBS incidence tends to decline in older women. This may be due to menopause-related reduction in oestrogen.





Visceral sensitivity is a characteristic of IBS. Oestrogen is known to regulate visceral sensitivity, as well as gut motility and psychological conditions which are collectively characteristics of IBS.⁴⁸

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Menstruation



How does the menstrual cycle impact the gut, and vice versa?

Sex hormone receptors are located in gastrointestinal cells. Fluctuating levels of hormones, specifically oestrogen and progesterone, can be responsible for cyclical changes to gastrointestinal function and symptoms throughout the menstrual cycle as both affect gastric motility (i.e. movement of food through the body) and gut permeability via these receptors present in the gut.⁴⁷ This can manifest as different gastrointestinal symptoms during distinct phases of the menstrual cycle (see below).⁴⁹⁻⁵²



Does the contraceptive pill affect the gut microbiota?

The combined contraceptive pill contains the hormones oestrogen and progestogen (see Figure 2). Some small human studies have seen modest differences in gut microbiota composition and diversity of females who use oral contraception compared to those that do not.^{53–54} However, more research is needed to understand its impact on gut health and the specific function of bacteria present in greater or smaller amounts following acute or chronic contraception use.



Figure 2. Hormonal fluctuation while taking an oral contraceptive containing both oestrogen and progesterone.⁴¹

Chidi-Ogbolu & Baar (2019) Front Physiol, 9: 1834.

LH: Luteinizing hormone FSH: Follicle-stimulating hormone

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The Gut Microbiota and Reproductive Health

Polycystic ovary syndrome (PCOS) and endometriosis are reproductive conditions which are commonly experienced by females, and may be influenced by alterations in the gut microbiota.



PCOS is a common condition which affects how a woman's ovaries work. Approximately **8–13% of reproductive-aged women struggle with PCOS** and up to 70% of affected women remain undiagnosed worldwide.⁵⁵ The **exact cause is unknown**; however it is often hereditary, and symptoms include:



How is the gut microbiota associated with PCOS?

Excess levels of androgen (a predominant male sex hormone) is one of the main signs of PCOS and the gut microbiota plays a role in regulating this hormone.⁵⁶ Lower gut microbiota diversity and dysbiosis are common features of PCOS.^{57–60} Gut dysbiosis increases intestinal permeability and is associated with elevated androgen production and inflammation which contribute to PCOS. A number of systematic reviews and meta-analyses have investigated the potential role of probiotics and synbiotics (probiotics and prebiotics combined) to help treat PCOS.^{61–64} While it remains difficult to identify optimal probiotic strains, *Lactobacillus* and *Bifidobacterium* are commonly used in studies.

"Evidence suggests that probiotics or synbiotics may improve testosterone levels, decrease inflammation, and improve insulin resistance and blood glucose levels in women with PCOS, in turn improving fertility in these women. Much more research needs to be done in this area, but taking a probiotic with a Lactobacillus strain may help to support fertility outcomes for some people – in addition to eating plenty of fruit, vegetables, nuts, seeds, and wholegrains to promote a healthy gut microbiome."



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Ro Huntriss RD Founder of Fertility Dietitian UK and author of 'Deliciously Healthy Fertility'

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The Gut Microbiota and Reproductive Health

Endometriosis

Endometriosis is a **chronic inflammatory disease** in which tissue similar to the lining of the uterus grows outside of the uterus. It can cause **severe pelvic pain**, particularly during menstruation, and can lead to **fertility issues**. The disease can affect women of any age, including teenagers.

Currently, endometriosis affects roughly **10%** (190 million) of reproductive age women and girls globally,⁶⁵ and up to 50% of women who are infertile.⁶⁶

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The cause of endometriosis remains unknown. Several theories have been suggested, including **genetic** factors, **immune system dysregulation**, and the spread of **endometrial cells** through the bloodstream or lymphatic system. However, none of these theories fully explain why endometriosis happens; it is likely the condition is caused by a combination of different factors.⁶⁵

How is the gut microbiota associated with endometriosis?

Recently, there has been increasing evidence suggesting an association between the gut microbiota and endometriosis.^{67–69} Animal studies have shown **alterations in the gut microbiota in endometriosis**, which may impact **disease onset and progression**.^{60'70} While the exact mechanisms of action are not fully understood, oestrogen levels, immunity or inflammation which are modulated, at least in part, by the gut microbiota and the oestrobolome, may play a role.^{69'71–72}

What is the treatment for endometriosis?

Current treatments for endometriosis primarily focus on symptom management with medications such as ibuprofen and paracetamol. However, targeting the gut microbiota through dietary and lifestyle factors may also help but more research is needed in this area. For example, a Mediterranean-style diet rich in fibre and polyphenols, both of which are known to increase gut microbiota diversity, show promise in helping manage symptoms.⁷³⁻⁷⁴



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Fertility



Research investigating the relationship between the gut microbiota and female reproductive health, including infertility, is still in its infancy.

A handful of studies have suggested that **gut dysbiosis** (an imbalanced and low diversity gut microbiota composition, favouring pathogens and proinflammatory bacteria) in both females and males could be linked to **infertility**.



For instance, pre-clinical and observational studies have provided evidence of a correlation between alterations in gut microbiota composition and infertility.²⁰¹⁷⁵⁻⁷⁹ However, concrete proof supporting the causal relationship is still lacking, although emerging research, particularly regarding male infertility, shows promise.²⁰¹⁷⁹

In females, it has been suggested that dysbiosis of the gut could potentially lead to **vaginal and uterine dysbiosis** which negatively affects **endometrial receptivity** at the time of implantation.^{80–81} For a deeper dive into the mechanisms of action between the gut microbiota and male/female (in)fertility, see Fabozzi et al. (2022).⁸²

Evidence also suggests there is an **association between undiagnosed**, and **therefore untreated**, **coeliac disease and unexplained infertility**.^{83–84} One explanation offered for this is that individuals with coeliac disease who do not follow a gluten-free diet may experience issues with nutrient absorption, leading to deficiencies that could affect fertility. Further research is needed to better understand and support the relationship between the composition and diversity of the gut microbiome and fertility.



Is there a connection between the vagina microbiota and fertility?

Dysbiosis of the vagina microbiota has been associated with various adverse reproductive events,⁸⁵⁻⁸⁶ including miscarriage.⁸⁷⁻⁸⁸ Lactobacillus has been seen to dominate the vagina microbiota of healthy women of reproductive age.⁸⁹ Low levels of Lactobacillus have been linked with IVF implantation failure.⁹⁰ Whilst the cause of miscarriage can be complex and multifactorial, more research is required to understand possible links with the vagina microbiota.

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Dietary Advice for Fertility

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Nutrition can impact various elements of the fertility journey including egg quality, sperm quality, IVF success and miscarriage implications.



Encourage a diet high in **fruits, vegetables, wholegrains and pulses** (e.g. beans, lentils) which contain a wealth of micronutrients, including fibre, and may improve fertility.



Focus on foods high in **monounsaturated fatty acids** (e.g. nuts, avocado) and **omega-3 fatty acids** (e.g. nuts, seeds and oily fish such as salmon, sardines and mackerel), which can improve egg and sperm quality, and are associated with improved IVF outcomes.⁹¹



Advise against or limiting **alcohol** consumption as it can adversely affect ovulation and sperm motility.



Suggest limiting **caffeine** intake, as high levels may negatively impact female fertility.



Recommend limiting foods high in **saturated fat** or **ultra-processed** as these have been linked to fertility issues.



Folate/ folic acid is important not only to help prevent **neural tube defects** but has also been associated with **healthy ovulation, shorter time to pregnancy and greater success with infertility treatment**.⁹² A daily **400 micrograms folic acid supplement** is recommended alongside dietary folate sources such as spinach, kale, Brussels sprouts, cabbage, broccoli, beans, fortified foods (e.g. some breakfast cereals), nuts, seeds, oranges, wholegrain foods, eggs and poultry.

"It's worth noting that nutrient deficiencies can play a role in fertility. For example, a vitamin B12 deficiency is linked with infertility. The good thing about that is by dietary changes or supplementation we can get rid of those deficiencies and then fertility outcomes can improve as a result."

Ro Huntriss, Registered Dietitian

Microbiome Matters Podcast (Season 6, Episode 4)





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Pregnancy



The Gut: Early Pregnancy

Progesterone and oestrogen rise during pregnancy which can lead to constipation by slowing down gastric emptying and increasing the risk of haemorrhoids (also known as piles) due to straining when going to the toilet.^{93_94} Other gastrointestinal symptoms during pregnancy may include heartburn, nausea and vomiting.



The Gut: Later Pregnancy



During the later stages of pregnancy, oestrogen levels peaks, leading to microbial changes. The composition and diversity of the gut microbiome has been shown to differ between healthy and complicated pregnancies, with dysbiosis associated with conditions such as gestational diabetes, preeclampsia and restricted foetal growth.^{95_96}

Postpartum Depression and the Gut Microbiome

Postpartum depression (PPD) is one of the common complications of childbirth, occurring in **10%–15% of women**. It's mainly characterised by depression, sadness, frustration, crying, irritability, hallucinations, suicidal thoughts, and a series of symptoms of mental disorders.^{97–98} While the exact origin and development of the disease is not fully understood, the relationship between the gut microbiome and PPD through the **gut-brain axis** has attracted much attention in recent years.⁹⁹

Differences in **gut microbiota** are evident between pregnant women with PPD and those without PPD.¹⁰⁰ It has been suggested that such disturbances in the gut microbiota of women with PPD are associated with the **disruption of multiple signalling pathways** and systems that ultimately lead to PPD development.⁹⁹ For example, in addition to the altered gut microbiota, the microbial-derived metabolites (i.e., short-chain fatty acids), including those associated with bile acids and tryptophan metabolism, are reported to be altered accordingly.⁹⁹



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Menopause



2



Perimenopause: The transition to menopause, characterised by erratic menstrual cycles (see Figure 3), can last anywhere between 1 to up to 10 years. Periods may occur less or more often, last longer or shorter and bleeding may be heavier or lighter than normal.

Menopause: Usually happens between the ages of 45-55 years, it is defined as the absence of menses (bleeding period) for 12 consecutive months, marking a significant change to hormones. During this time, levels of oestrogen and progesterone decrease (see Figure 3) while the stress hormone cortisol increases. After menopause, adipose tissue becomes the primary source of remaining oestrogen.¹⁰¹



Menopausal symptoms vary and appear gradually. Common symptoms include:



The decrease in oestrogen also increases the risk of **osteoporosis** and **cardiovascular disease**.

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Menopause



Gut Microbiota Changes During Menopause



As individuals age, gut microbiota diversity tends to decline.²³ **Postmenopausal women have lower gut microbiome diversity** and altered overall composition compared to premenopausal women as well as a **decreased abundance of gut microbial beta-glucuronidase**, the enzyme involved with oestrobolome (see page 4).²²



During menopause, the gut microbiome becomes **more similar to the male gut microbiome**.^{21/102} Specifically, there is an increase in the Firmicutes:Bacteroidetes ratio after menopause.¹⁰³ There is a greater abundance of *Butyricimonas, Dorea, Prevotella, Sutterella* and *Bacteroides*, and lower number of *Firmicutes* and *Ruminococcus* in postmenopausal women. However, **more research is needed** to fully understand the specific functions and health implications of these bacterial changes.²¹



A decrease in the relative abundance of **short-chain fatty acid (SCFA) producing bacteria** is observed in postmenopausal women.¹⁰³ It has also been shown that postmenopausal women have fewer specific **gut pathogens** and reduction in the **hormone-related metabolic potential of the gut microbiome**.



Via the **oestrobolome**, gut microbes may participate in sex hormone reactivation and retention in postmenopausal women to help counteract the sharp drop in oestrogen.²² Therefore, ensuring gut microbiome diversity is key to support this.



Hormone replacement therapy (HRT) is a treatment used to help alleviate menopause symptoms. It replaces the decreased hormones oestrogen and progesterone and research suggests **HRT reduces gut microbiota dysbiosis**.¹⁰⁴



There are a number of factors (modifiable and non-modifiable) which affect the diversity of the gut microbiota including **diet**, **stress**, **sleep quality**, **physical activity**, **smoking status** and **medication** (see pages 15-16).

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Menopause



The exact **mechanisms of action** between the gut microbiota and sex hormones are not fully understood. However, research suggests it may be due to:

- Sex hormones serving as substrates for microbial metabolism which influence the gut microbiota.²¹
- Decrease in oestradiol and progesterone which can suppress the immune system thereby increasing susceptibility to pathogens.^{21–22}
- Altered concentrations of minerals in the gut that are required for bacterial growth, e.g., less calcium due to a decrease in oestradiol.¹⁰⁵
- Altered gastrointestinal motility due to loss of progesterone which is an important determinant of the gut microbiome.²¹

More research is needed in large study populations to fully understand the associations between female sex hormones and gut health as well as the mechanisms underlying these associations.

There are many knowledge gaps, including the role the gut microbiome plays in menopause-related disease risks, and whether menopausal hormone therapy (e.g. HRT) modifies menopause-related change in the gut microbiome.

Gut-Brain Axis

The gut microbiome regulated sex hormones. Sex hormones, particularly oestrogen, affect the brain and can play an important role in influencing **brain function and behaviour**.⁴⁰¹¹⁰⁶⁻¹⁰⁷ Oestrogen receptors are present across the central nervous system, with the brain's **hippocampus** (which is responsible for **memory, learning and emotions**) containing many of these receptors. Therefore, changes in sex hormone levels during key life stages, such as menopause, can cause changes to brain function.¹⁰⁸



Is there a link between the gut microbiome and weight gain during menopause?

It is common for women to gain weight during menopause. This can be attributed to various factors such as changes in muscle mass, gut microbiota, metabolism and lifestyle factors e.g., activity levels and sleep. A reduction in gut microbiome diversity can lead to lower production of SCFAs, which play a role in appetite regulation through the gut-metabolism axis.¹⁰⁹

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Dietary Advice for Menopause



Diet and lifestyle factors (e.g. stress, sleep quality, physical activity, smoking status and medication) can play a role in helping to **alleviate or reduce menopause symptom severity**. While specific dietary advice targeting gut health during menopause is limited, most recommendations emphasise promoting **bone and heart health**, which often overlaps with factors that also positively impact gut health.



Digestive Health

- Encourage a **healthy, well-balanced diet, rich in fibre** from plant foods to support digestive and heart health, including fruits, vegetables, wholegrain carbohydrates, beans, lentils, nuts and seeds. Use our Gut Health Habit Tracker to check off your weekly plant points email science@yakult.co.uk for free hardcopies.
- Discuss **triggers** that can cause hot flashes e.g. spicy foods, alcohol and hot drinks.

Muscle & Bone Health

- Advise including **calcium rich foods** e.g. dairy (milk, cheese etc), green leafy vegetables (except spinach which contains high levels of calcium but the body cannot fully digest), fortified plant-based milk alternative drinks, bread made with fortified flour, sardines and pilchards.
- Recommend a daily vitamin D supplement (10 micrograms) during autumn and winter months.



Heart Health

- Encourage limiting **saturated fat** intake (e.g. fatty meats, butter, cheese, cakes and biscuits) and replace with unsaturated fat (e.g. olive oil, rapeseed oil, avocados, nuts, seeds and oily fish).
- Suggest reducing **salt intake** to lower cardiovascular risk. Ready meals, sauces, soups and processed meats are often higher in salt. Recommend seasoning food with herbs and spices rather than salt.

Is it useful to include plant oestrogens in your diet during menopause?

Women in Asian countries who typically consume a phytoestrogen-rich diet (i.e. linseeds, tofu, edamame beans, yoghurt and pulses) tend to experience fewer menopausal symptoms than Western women.¹¹⁰ However, overall the evidence has been mixed on whether phytoestrogens can help with hot flushes. It can take 2-3 months for any benefits to be seen and their effectiveness varies between women, potentially due to differences in gut microbiome composition and diversity. More conclusive evidence is required for their potential effects on other menopausal symptoms such as brain fog.

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Lifestyle Advice for Menopause





Exercise: Encourage regular moderate exercise, especially weight bearing activity and muscle strengthening exercises. Physical activity impacts muscle and bone maintenance, heart health, weight management, sleep quality, concentration, symptom management (e.g. hot flushes) and can provide mental health benefits.



Sleep: While menopausal symptoms can reduce sleep quality and comfort, irregular sleep patterns are associated with poorer diet quality,¹¹¹ inflammation and reduced gut microbiota diversity. Recommend avoiding large meals before bedtime, keeping a consistent sleep schedule and avoiding strenuous exercising or using electronic devices with bright lights close to bedtime.



Mindfulness: Suggest incorporating relaxation techniques. Anxiety and depression are common during menopause due to hormonal changes which can also manifest in the form of gut-related complaints.

Knowledge is Power

If your patients are struggling with digestive issues, keeping a symptom diary can help highlight any possible patterns or symptom triggers which could then be discussed with a healthcare professional. Check out www.loveyourgut.com/help-and-resources for a 'Food, Mood & Symptoms Diary' for your patients.



"Hormones can be effectively harnessed through the choice of a balanced combination of exercise, nutrition and sleep. Discussing options with your patients and encouraging them to make their own informed and personal choices are far more likely to enable them to take responsibility for their health and adhere to changes in lifestyle that are beneficial for their health."



Dr Nicky Keay Author of 'Health Hormones and Human Potential'

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