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The potential role of the Mediterranean diet for the treatment and management of polycystic ovary syndrome: a review of the pathophysiological mechanisms and clinical evidence

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Abstract

Polycystic ovary syndrome (PCOS) is a common endocrine disorder amongst reproductive-aged women associated with cardiometabolic, reproductive and psychological abnormalities. Lifestyle modification, including a healthy diet, is considered first-line treatment for management of clinical symptoms. However, there is limited high-quality evidence to support one superior therapeutic dietary intervention for PCOS management that is beyond general population-based dietary guidelines. Adherence to a Mediterranean diet (MedDiet) has been shown to decrease cardiometabolic disease risk and attenuate depressive symptoms, particularly in patients with metabolic perturbations. This narrative review summarises the proposed biological mechanisms underpinning the potential therapeutic benefits of a MedDiet for the management of cardiometabolic, reproductive and psychological features related to PCOS. Observational evidence suggests an inverse relationship between MedDiet adherence and PCOS features, particularly insulin resistance and hyperandrogenemia. Although the exact mechanisms are complex and multifaceted, they are likely related to the anti-inflammatory potential of the dietary pattern. These mechanisms are underpinned by anti-inflammatory bioactive constituents present in the MedDiet, including carotenoids, polyphenols and n-3 polyunsaturated fatty acids (PUFAs). Synthesis of the available literature suggests the MedDiet could be a promising therapeutic dietary intervention to attenuate short and long-term symptoms associated with PCOS and may aid in reducing the longer-term risks associated with cardiometabolic diseases and reproductive and psychological dysfunction. Nevertheless, current evidence remains insufficient to inform clinical practice and well-designed clinical trials are needed. As such, we provide recommendations for the design and delivery of future MedDiet interventions in women with PCOS, including exploring the acceptability, and feasibility to enhance adherence.

Polycystic ovary syndrome (PCOS) is a common and heterogenous endocrine disorder, affecting approximately 8–13% of females of reproductive age[1]. It is a multifaceted syndrome characterised by a broad range of clinical symptoms, exerting both physical and psychological health-related consequences over the lifespan[2,3]. Diagnosis of PCOS typically includes a combination of medical history, the exclusion of other conditions with similar symptomology, clinical examination and biological testing. The 2023 PCOS International Guidelines recommend that an adult diagnosis requires the presence of two of the three following features (with the exclusion of other causes); (1) oligo-/anovulation, (2) clinical or biochemical hyperandrogenism, (3) polycystic ovarian morphology identified via ultrasound or testing of anti-Mullerian hormone[4]. In contrast, the recommended diagnosis for adolescent girls requires both oligo-/anovulation and clinical or biochemical hyperandrogenism and excludes the testing of ovarian morphology[4].

Underpinning many of the negative consequences of PCOS is a reduction in insulin sensitivity coupled with high levels of androgens[2,3,5]. Women with PCOS are at an elevated risk of developing a range of health complications, including type 2 diabetes mellitus (T2DM), metabolic syndrome[2,6] and cardiovascular disease (CVD)[7,8]. Beyond these health concerns, PCOS significantly affects reproductive health, manifesting in symptoms such as infertility[9], irregular or absent menstrual cycles and adverse neonatal and pregnancy outcomes including gestational diabetes, miscarriage and pre-eclampsia[10–12]. The syndrome also has a notable impact on psychological health and wellbeing with an increased prevalence of disordered eating

behaviours, including binge eating[13,14] as well as heightened rates of anxiety and depression which negatively impacts health-related quality of life and self-efficacy[14–17]. Although the mechanisms associated with insulin resistance (IR) in PCOS are largely independent of body weight, IR is still exacerbated by excess body weight[5,18–20] and central adiposity, further heightening clinical symptoms and cardiometabolic risks[21–23]. Women with PCOS also have a greater propensity for longitudinal weight gain[21,23]. Therefore, weight loss and/or weight management is thought to be one of the most important therapeutic treatment strategies for the management of PCOS and is typically the focus of many lifestyle interventions[24]. While weight loss improves many of the clinical features of PCOS[25], it is important to appreciate that IR also affects women with PCOS who present within a healthy-weight range (in accordance with normal BMI classifications)[26]. Therefore, as recommended in the international evidence-based guidelines for management of PCOS, lifestyle modifications which include adopting a healthy dietary pattern coupled with regular physical activity are considered first-line treatment for both weight management and better manage health outcomes associated with cardiometabolic disease risk, reproductive and psychological health[27]. However, the optimal dietary approach remains controversial with limited high-quality evidence to support one specific dietary approach beyond traditional population-based dietary guidelines[28–30]. Nevertheless, dietary interventions which promote healthy long-term behaviour change, without necessarily focusing on weight loss and caloric restriction, may assist in improving psychological health[31], and help facilitate adherence and maintenance to longer-term lifestyle and behavioural change. Therefore, to accommodate individual patient needs and health goals, defining the optimal dietary approach (with or without caloric restriction) for the management of PCOS is of clinical interest.

A Mediterranean diet (MedDiet), which is often described as an anti-inflammatory or plant-based dietary pattern, is typically characterised by a high consumption of fruits, vegetables, legumes, wholegrains and liberal use of extra-virgin olive oil (EVOO); moderate consumption of fermented dairy, eggs and red wine (consumed with meals only); and a low and/or infrequent consumption of red meat and meat products, butter, vegetable oils and processed foods[32]. The traditional dietary pattern was first investigated among the people living in the olive-growing regions of the Mediterranean basin before the mid-1960s. Nevertheless, because of the variability in cuisine and dietary constituents which define traditional dietary behaviours of inhabitants of the Mediterranean basin, a singular MedDiet does not exist[33]. Nevertheless, despite potential differences in the operationalisation of a MedDiet, being predominantly plant-based, the dietary pattern is naturally low in ultra-processed foods, sugar and saturated fat and rich in several functional components, including vitamins and minerals, carotenoids, unsaturated fatty acids and phenolic compounds, depicted by antioxidant and anti-inflammatory properties[34].

There is substantial evidence supporting the efficacy of a Mediterranean diet (MedDiet) on cardiometabolic perturbations in other populations with similar risk profiles as those observed in PCOS. Specifically, adherence to a MedDiet is inversely associated with central obesity in epidemiological studies and is associated with weight loss, with or without caloric restriction, in dietary intervention studies[35,36]. Moreover, adherence to a MedDiet has been shown to improve insulin sensitivity, glycemic control and attenuate depressive symptoms, particularly in patients with metabolic perturbations[37]. Nevertheless, evidence from well-designed and robust clinical trials investigating the efficacy of a MedDiet to ameliorate PCOS symptoms is scant. However, evidence from well-designed and robust clinical trials investigating the efficacy of a MedDiet to ameliorate PCOS symptoms is scant. As such, this review aims to elucidate the proposed biological mechanisms underpinning the potential therapeutic benefits of a MedDiet for the management of features related to PCOS.

Features of PCOS

Cardiometabolic

The pathophysiology of cardiometabolic disease risk in PCOS is complex and multifaceted, involving interplays between hormonal imbalances, IR, chronic low-grade inflammation and obesity. IR is a hallmark feature of PCOS and occurs in at least 75% of cases, independent of body weight, resulting in impaired glucose metabolism[38]. The proposed primary mechanism for IR in women with PCOS involves an increase in serine phosphorylation, causing post-binding defects in insulin signalling[39]. Alternate mechanisms of IR include decreased glucose transporter 4 (GLUT4) in subcutaneous adipocytes, decreased hepatic clearance of insulin, mitochondrial dysfunction and activation of serine kinases in the mitogen-activated protein kinase/extracellular signal-regulated kinases (MAP-K) pathway[39]. This subsequent hyperinsulinemia increases the risk of T2DM and is closely related to central obesity, dyslipidaemia and hypertension, forming a clustering of cardiometabolic abnormalities. Approximately 30% of women with PCOS have impaired glucose tolerance and 7.5% have T2DM[40] with the degree of risk to the onset of T2DM varying from between three to five-fold, contingent upon obesity and ethnicity[41]. Women with PCOS also exhibit an insulin paradox whereby ovarian and adrenal tissues remain sensitive to the stimulatory effects of insulin, despite displaying metabolic IR[42]. Moreover, independent of IR, excess body weight, particularly central adiposity, also exacerbates metabolic and CVD risks by promoting dyslipidaemia, hypertension and a pro-inflammatory state, contributing to the formation and development of atherosclerosis and subsequent CVD risk[43,44]. As such, the metabolic syndrome is also an important feature observed in PCOS[45].

Reproductive

The reproductive dysfunction observed in PCOS, encompassing irregular menstrual cycles, anovulation and subfertility, originates from an intricate interaction among hormonal dysregulation, IR and putative inflammatory pathways. Notably, PCOS emerges as the principal aetiology of anovulatory infertility across the lifespan of the female[46]. Furthermore, infertility afflicts 70–80% of individuals diagnosed with PCOS[47].

A common characteristic of PCOS is elevated levels of androgens[48]. While the precise physiological pathways remain elusive, prevailing evidence suggests that the ovaries and adrenal glands constitute the primary androgen sources in females[49,50]. In the ovaries, the synthesis of androgens is predominantly regulated by the ovarian theca cells, with contributions from the mesenchymal cells[51]. However, PCOS is characterised by an abnormal androgen secretion, culminating in hyperandrogenism[52]. Hyperandrogenism can disrupt follicular growth and gene expression in oocytes, theca and granulosa cells, potentially contributing to folliculogenesis complications and anovulation[53–55].

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In addition, IR and hyperinsulinemia can further escalate androgen levels, thereby intensifying hyperandrogenism and additionally impairing ovarian functionality.

Notably, the MAP-K insulin pathway remains unaffected by IR; rather, it is the compensatory hyperinsulinemia that augments androgen steroidogenesis in the thecal cells, thereby impeding follicular development[56,57]. The vicious cycle of obesity, IR and increased androgen production exacerbates hyperandrogenism[51]. Women with PCOS exhibit a higher volume of visceral adipose tissue compared to their non-PCOS counterparts, which is positively correlated with total androgen levels[58]. Comparative analyses reveal that women who are overweight exhibit significantly elevated androgen levels relative to their healthy-weight peers[59]. Increased body weight correlates with reproductive dysfunction and lower oocyte quality, affecting implantation rates and oocyte retrieval during assisted reproduction, particularly in cases of central obesity[60–62].

Alterations in normal ovarian follicle development are also a hallmark feature in PCOS, with the ovaries developing numerous small, immature follicles that fail to progress to ovulation.[63]. This anomaly commonly termed 'polycystic ovaries', is observable via ultrasound and constitutes one of the diagnostic criteria for PCOS[4]. Disrupted folliculogenesis leads to irregular or absent menstrual cycles (oligomenorrhea or amenorrhoea), a defining feature of PCOS, and adversely affects fertility due to the lack of ovulation. This phenomenon is attributed to a dysregulated balance of pituitary gonadotrophins, with elevated luteinizing hormone (LH) to follicle-stimulating hormone ratio, resulting in an increase of androgens and decreased oestrogen expression, culminating in disordered folliculogenesis, immature follicles, thus promoting infertility[51].

Chronic low-grade inflammation may also impair fertility by impeding oocyte maturation[64,65]. Obesity, IR and hyperandrogenism are thought to collectively contribute to the pro-inflammatory state observed in women with PCOS[66]. The follicular microenvironment, pivotal for ovarian function, is adversely affected by the presence of pro-inflammatory cytokines including TNF-a, IL1-B, IL-6[67]. This low-grade inflammatory state within the follicular microenvironment may disrupt folliculogenesis by inducing oxidative stress in the ovaries[68,69] which is likely magnified by the presence of obesity[69].

Psychological

Women with PCOS have a heightened prevalence of depression (2.3-fold) and anxiety (4-fold) compared to those without PCOS[15]. The aetiology of these psychological disturbances remains unclear, implicating a multifactorial interplay among biological, psychological and socio-environmental determinants.

Neurotransmitter dysregulation observed in PCOS, specifically reduced inhibitory neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid and acetylcholine, may disrupt the hypothalamic-pituitary-adrenal (HPA) axis and predispose individuals to depression[70,71]. Concomitantly, an augmentation in neurotransmitters which elevate LH has been observed in PCOS, which could further precipitate depressive symptoms[71,72] by causing the theca cells in the ovary to produce excessive androgen and exacerbate the progression of PCOS[73]. Moreover, hyperactivity of the HPA axis, observed in approximately 50% of major depressive disorder cases, contributes to depression through hypercortisolemia[74]. Lastly, psychological stressors trigger an inflammatory response, increasing pro-inflammatory cytokines associated with depression and exacerbating PCOS symptoms[75–77].

Although the exact mechanisms remain unclear, IR is another potential mediator, independently associated with depression in PCOS[78]. Specifically, higher Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) scores correlate with a 2.3-fold increased risk of depression[78], possibly due to disruptions in insulin signalling affecting brain regions which influence mood[73].

Clinical manifestations of PCOS, including hirsutism, acne and alopecia, significantly impact self-esteem and body image[79], contributing to psychological distress such as depression, anxiety and social phobia[15,80–83]. Body dissatisfaction is also prevalent among women with PCOS, exacerbated by the high prevalence of obesity in this clinical population, which also correlates with disordered eating behaviours, such as binge eating[84–86].

In addition, up to 70% of patients with PCOS experience infertility[87], of which the clinical pregnancy rate using in vitro fertilisation and embryo transfer technology is low[88]. Infertility treatments, such as in vitro fertilisation, can exacerbate psychological distress through hormonal interactions impacting serotonin levels[89].

Given the established role of PCOS as a predominate factor in infertility, this condition presents significant challenges to reproductive health and psychological wellbeing, contributing to psychosocial distress[90] and negatively impacting health-related quality of life[91].

Potential benefits of a Mediterranean diet for the management of features related to PCOS. From evidence to proposed mechanisms

At present, the majority of the literature related to MedDiet adherence and features of PCOS are observational studies with relatively small samples (Table 1). Furthermore, many of these studies are conducted within Mediterranean populations where adherence to the diet is expected to be greater relative to non-Mediterranean populations, thus limiting the generalizability of the study findings. Nevertheless, there is evidence from Mediterranean populations showing low to moderate adherence to a MedDiet in recent years[95] However, whether this reflects a true decrease in adherence given the absence of a universally accepted adherence tool and the marked heterogeneity and psychometric properties of each of the available adherence tools is unknown[96]. At present there are a number of diet quality indices used to quantify MedDiet adherence[97], therefore making comparisons between studies challenging. For example, dietary adherence tools such as the alternate Mediterranean Food Score or the original Mediterranean Diet Score are dependent on the usual dietary characteristics of the studied population and may not reflect true adherence to a traditional MedDiet, particularly in non-Mediterranean populations. Furthermore, adherence tools that are based on normative criteria and reflective of a traditional MedDiet, such as the Mediterranean Diet Adherence Screener are also not without limitations, particularly when applied in non-Mediterranean populations given that it was developed and validated for application in Spanish middle-aged and older adults (aged 55–80 years) at a high risk of coronary heart disease, thus potentially limiting its utility and generalizability[98].

Nevertheless, the absence of well-designed published clinical trials exploring the efficacy of a MedDiet intervention in women with PCOS represents an important gap in the research literature. In one of the only published randomised controlled trials, Mei et al[99] showed that an energy-restricted low-carbohydrate Mediterranean-style diet was superior in restoring menstrual

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Table 1. Characteristics of studies investigating the Mediterranean diet on clinical features of polycystic ovary syndrome

Author	Primary aim	Country of origin	Study design	Study population & sample size	Primary outcomes
Barrea et al 2019[92]	To assess the association between MedDiet adherence and clinical severity of PCOS	Italy	Cross-sectional	$n = 224$ women ($n = 112$ with PCOS; $n = 112$ controls) aged 18-40 years, BMI 18.5-39.9 kg/m^2 and free from underlying cardiometabolic disease	Greater adherence to a MedDiet was inversely associated with IR and hyperandrogenemia
Cutillas-Tolín et al 2021[93]	To explore associations between diet quality indices and the presence of PCOS features	Spain	Case-control	$n = 285$ women ($n = 126$ with PCOS; $n = 159$ controls) aged 18-40 years	Adherence to a MedDiet was protective against clinical phenotypic features of PCOS, namely hyperandrogenism and oligo-anovulation
Barrea et al. 2021[94]	To characterise the determinants of the metabolic health status in obese women with PCOS	Italy	Cross-sectional	$n = 94$ women with PCOS; aged 18-30 years, BMI ≥30 kg/m^2 and free from underlying cardiometabolic disease	Poor adherence to a MedDiet was associated with a 'metabolically unhealthy obesity' as defined through evaluation of endocrine-metabolic profiles, inflammatory status, cardiometabolic indices and body composition parameters.
Mei et al 2022[99]	To determine the therapeutic benefits of an energy-reduced low-CHO, Mediterranean-style diet, compared with a standard low-fat diet, on reproductive, endocrine and cardiometabolic parameters in overweight and obese patients with PCOS	China	Randomised control trial (12-week intervention)	$n = 59$ (low-CHO, MedDiet, $n = 29$; standard low-fat, $n = 30$) overweight (BMI ≥24 kg/m^2) women with PCOS without underlying cardiometabolic disease, free from use of non-progesterone hormonal medication, insulin sensitisers or lipid-lowering medications within the previous 3 months and not planning for pregnancy or no use of contraceptive pill during the intervention period	Both dietary interventions were effective in improving anthropometric, reproductive and cardiometabolic parameters; however, the energy restricted low-CHO Mediterranean-style diet was superior in restoring menstrual regularity, lowering body weight, waist circumference and improving fasting blood glucose, insulin sensitivity, total testosterone and luteinizing hormone
Foscolou et al. 2024[104]	To investigate the potential benefits of a personalised MedDiet intervention, compared with a standard lifestyle intervention, on optimising nutritional status and attenuating symptoms of anxiety in adolescent girls diagnosed with PCOS	Greece	Randomised control trial (12-week intervention)	$n = 40$ (MedDiet, $n = 20$; standard lifestyle intervention, $n = 20$) adolescent females aged 15–17 years free from severe illness, psychiatric disorders, following a specific diet within the previous 5 years or use of nutritional supplements within the previous 6 months.	A personalised MedDiet intervention, when compared against a standard lifestyle intervention, was more effective at improving diet quality (i.e., decreased energy intake, total fat, SFA, and increased intake of dietary fibre and MUFA), attenuating symptoms of anxiety, reductions in body weight, body fat and triglycerides.

Abbreviations: MedDiet, Mediterranean diet; PCOS, polycystic ovary syndrome; IR, insulin resistance; CHO, carbohydrate; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid.

regularity, lowering body weight, waist circumference and improving fasting blood glucose, insulin sensitivity, blood lipids, total testosterone and luteinizing hormone when compared against an energy-restricted low-fat diet in $n = 59$ Chinese women with PCOS and overweight or obesity. Although these results are indeed promising, irrespective of being identified as a Mediterranean-style diet, the dietary protocol described in the aforementioned study was not reflective of a Mediterranean-stye diet. For example, MedDiet principles (e.g., high intake of fruits, vegetables, legumes, nuts and EVOO) were combined with a low-carbohydrate diet, consisting of less than 100 g per day. Moreover, the dietary intervention was also calorie-restricted. As such, it is plausible that any potential benefits observed may have been attributable to the caloric-restricted, low-carbohydrate component of the intervention, thus diluting any potential mechanistic benefit of the MedDiet. In general, dietary interventions targeted for women with PCOS and overweight or obesity are typically designed to create a caloric deficit to elicit weight loss. However, achieving caloric restriction and weight loss targets in this cohort is challenging, when compared to women without PCOS[100]. Although achieving clinically significant weight loss (e.g., ≥5% of body weight) over short intervention periods has been documented in PCOS, attrition rates are almost 50% suggesting difficulties with adhering to calorie-restricted diets[101–103]. Lastly, few studies investigate the potential benefits of a MedDiet on psychological outcomes in women with PCOS. Foscolou et al[104] showed that a personalised MedDiet intervention, when compared against a standard lifestyle intervention, attenuated symptoms of anxiety in adolescent females with PCOS; however, to the best of our knowledge, this has yet to be thoroughly investigated in adult women.

Individual food groups and /or biologically active dietary constituents consistent with a MedDiet and their potential impact on cardiometabolic, reproductive and mental health have previously been reviewed[105–107]. However, given the synergistic relationship of nutrients within the complex matrices of an existing dietary pattern, several physiological mechanisms connecting MedDiet adherence with clinical features of PCOS are likely.

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Therefore, the evidence related to MedDiet adherence and cardiometabolic, reproductive and psychological outcomes and their proposed mechanisms, will be summarised herein.

Evidence from cardiometabolic outcomes

In the PREvención con DIeta MEDiterránea (PREDIMED) study, Estruch et al[108] reported a 30% risk reduction in major cardiovascular events over a 5-year period in patients at high risk of cardiovascular disease when assigned to either a MedDiet supplemented with EVOO (1 litre/week) or nuts (30 grams/day), compared to those assigned to a low-fat control diet. Furthermore, after 4 years of follow-up, participants assigned to either of the two MedDiets, without caloric restriction, had a 40% and 18% reduction, respectively, in the incidence of T2DM compared to those in the low-fat control diet[109]. Investigators from the CORonary Diet Intervention with Olive oil and cardiovascular PREVention (CORDIOPREV) study assessed the effects of a MedDiet versus a low-fat control on endothelial function, as assessed by flow-mediated dilation (FMD), in patients with established coronary heart disease[110]. Yubero–Serrano et al[111] reported that patients assigned to the MedDiet intervention had higher FMD and endothelial progenitor cells and decreasing endothelial microparticles, regardless of the severity of endothelial dysfunction. Moreover, the investigators also showed that adherence to a MedDiet intervention decreased intracellular ROS production, cellular apoptosis and endothelial cell senescence and increased cellular proliferation and angiogenesis.

Using a randomised cross-over study, Galie et al[112] assessed changes in plasma metabolites after following a MedDiet compared to the consumption of a singular healthy food (nuts) within the context of a non-MedDiet among participants with the metabolic syndrome. The investigators showed that adherence to a MedDiet, rather than consuming nuts in the context of a non-MedDiet, was significantly associated with changes in circulating metabolites (in particular lipids, acylcarnitines, amino acids, steroids and tricarboxylic acid (TCA) intermediates); importantly these changes were also related to improvements in participants' metabolic risk profile, independent of changes in body weight, including decreases in fasting glucose, insulin and HOMA-IR. Esposito et al[113] reported that after 2 years of follow-up, participants with the metabolic syndrome randomised to receive a MedDiet (without energy restriction) showed significant improvements in endothelial function and reduced markers of systemic vascular inflammation, independent of changes in body weight, compared to those randomised to a standard healthy diet congruent with dietary guidelines. In contrast, Salas-Salvado et al[114] reported significant improvements in cardiovascular disease risk factors including waist circumference, fasting glucose, insulin sensitivity, triglycerides and HDL cholesterol in participants enrolled in the PREDIMED-Plus lifestyle intervention, aimed at evaluating the effect of an energy-restricted MedDiet intervention, physical activity promotion and behaviour modification in overweight and obese middle-aged adults with the metabolic syndrome.

Similar improvements in metabolic risk profiles have also been observed in people with existing T2DM. When compared against participants' habitual diet, Itsiopoulos et al[115] showed that a 12-week *ad libitum* MedDiet intervention was associated with significant reductions in HbA1c levels. In patients newly diagnosed with T2DM, Esposito et al[116] showed that a lower carbohydrate MedDiet resulted in greater reductions in HbA1c levels and delayed the need for diabetes medications by ~2 years compared with a standard low-fat diet. Moreover, this effect was largely independent of weight loss. In sub-group analysis from the CORDIOPREV study, Gutierrez-Mariscal et al[117] reported that in newly diagnosed diabetic patients with coronary heart disease, long-term (5 years) consumption of a MedDiet intervention was associated with improved glycemic control and a higher probability of T2DM remission.

Evidence from fertility outcomes

Research shows that maternal preconception dietary behaviours may be related to fertility, as well as influence IVF outcomes, including oocyte and embryo quality, implantation and successful completion of pregnancy[118]. Nevertheless, there is a paucity of evidence to support specific dietary patterns or guidelines to improve fertility outcomes for women with much of the evidence linking diet to fertility largely based on studies of single nutrients, or individual food groups as opposed to whole dietary patterns, particularly for women undertaking IVF[119]. Moreover, much of this evidence is limited to observational study designs. In a prospective cohort study of $n = 244$ women without obesity (aged 22–41 years) undergoing a first IVF treatment, Karayiannis et al[120] reported that greater adherence to a MedDiet was associated with ~2.7 times higher likelihood of clinical pregnancy and live birth. Similar findings were also reported in a prospective cohort of women without obesity ($n = 357$) who underwent a total of 608 ART cycles, with the investigators reporting that women in the second and third quartiles of MedDiet adherence had higher probability of clinical pregnancy and live birth compared with women in the first quartile[119]. In a further observational study of $n = 700$ Chinese women about to commence IVF, greater adherence to a MedDiet was positively associated with greater embryo yield[121]. However, not all studies have described positive associations between MedDiet adherence and successful IVF outcomes, including clinical pregnancy, live birth, oocyte yield and embryo quality[122,123].

The menstrual cycle is also an important indicator of reproductive health and irregular menstrual cycles may indicate anovulation, and thus decrease the ability to conceive[124]. In a cross-sectional analysis of $n = 311$ Spanish female university students, Onieva-Zafra et al[125] reported that women with low adherence to a MedDiet had longer menstrual cycles than those with higher adherence. Moreover, upon further analysis of individual constituents of a MedDiet, women who consumed less than two pieces of fruit per day were more likely to suffer from menstrual pain; similar findings were also observed for women who infrequently consumed legumes (≤1 time per week)[125].

Evidence from psychological outcomes

An increasing body of evidence has emerged suggesting that diet quality may be an important modifiable risk factor for mental health disorders. In particular, evidence from systematic reviews and meta-analyses suggests that adherence to MedDiet is inversely associated with a risk of depression or depressive symptoms in both younger and middle-aged adults[126,127]. In addition to the growing body of observational research, the SMILES[128] and HELFIMED[129] studies were among the first two clinical trials to show that a MedDiet intervention can be effective at reducing depressive symptoms in adults with major depression or mild depressive symptoms. These findings have since been corroborated in a recent systematic review and meta-analysis of clinical trials[130]. Nevertheless, given the between-study heterogeneity,

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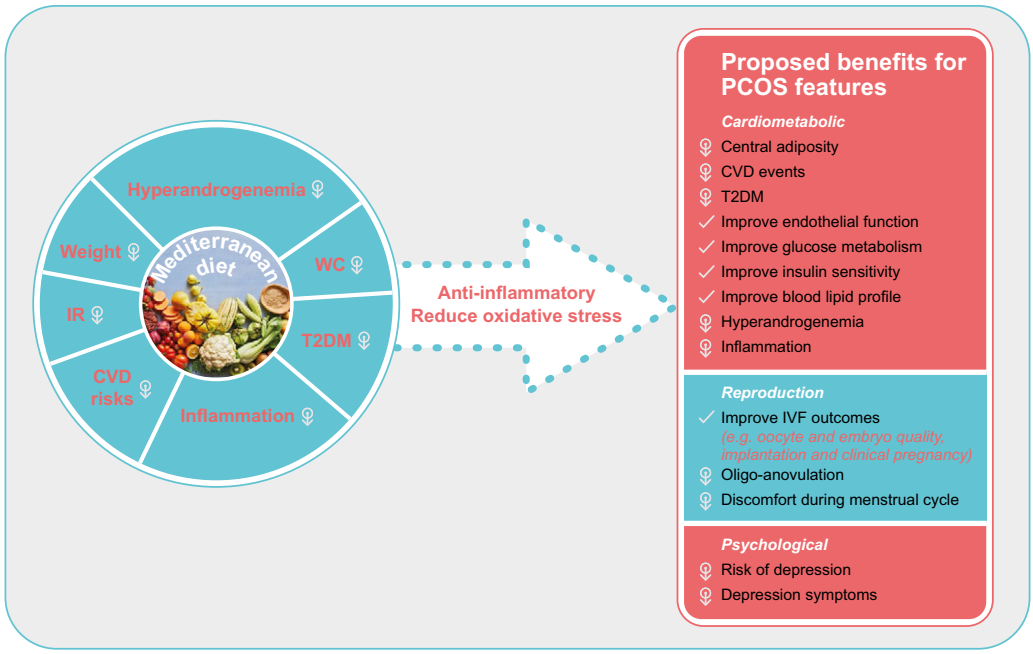

Fig. 1. The proposed mechanisms and benefits of a Mediterranean diet for features of polycystic ovary syndrome. IR: insulin resistance, CVD: cardiovascular disease, T2DM: type 2 diabetes mellitus, WC: waist circumference, IVF: in vitro fertilisation.

the investigators suggested a need for more robust, long-term randomised controlled trials (RCTs) in order to establish recommendations in clinical practice.

Potential therapeutic benefits of a Mediterranean Diet

Although the exact mechanisms by which a MedDiet exerts potential benefits on improving clinical features of PCOS remains to be elucidated, it is likely related to the anti-inflammatory potential of the dietary pattern, reductions in oxidative stress and a higher intake of antioxidants derived from the dietary pattern, as depicted in Fig. 1. The apparent anti-inflammatory benefits of a MedDiet have been shown in a number of clinical trials, including sub-group analysis of the PREDIMED study where adherence to both MedDiet intervention groups downregulated the expression of adhesion molecules on circulating T lymphocyte and monocyte surfaces, as well as inflammatory biomarkers (TNF-α, IL-6, MCP-1 and CRP) in serum[131–135]. As such, there is now a large body of evidence from observational and intervention studies that have identified an inverse relationship between plant-based dietary patterns and oxidative stress and pro-inflammatory biomarkers[136–139]. This is not surprising given that the MedDiet is predominantly plant-based and contain numerous anti-inflammatory constituents which may displace other dietary or food components (e.g., saturated fat, sugar and ultra-processed foods) which are known to elicit chronic inflammation and chronic disease. For example, flavonoids are biologically active polyphenolic compounds ubiquitously found in plant-based foods with antioxidant and anti-inflammatory effects[140,141]. Furthermore, carotenoids and polyphenols both act as potent scavengers of ROS, inhibit lipid peroxidation and modulate redox-sensitive transcription factors involved in the up-regulation of pro-inflammatory cytokines[142,143]. Specifically, they suppress pro-inflammatory molecules and modulate inflammatory pathways, including NF-κB, AMP-activated protein kinase (MAPK) and the arachidonic acid pathway[141]. For example, polyphenols from EVOO, the principal lipid source in a MedDiet, blunts pro-oxidant enzymes NOX-2 and NOX-4 and increases the expression of anti-inflammatory molecules including peroxisome proliferator-activated receptor-γ (PPARγ) mRNA[144]. Moreover, EVOO polyphenols also attenuate TNF-α-induced NF-κB activation and thus elicits a protective function on the endothelium, therefore protecting against arteriosclerosis and major cardiovascular events[145]. In addition, previous literature has shown that higher intakes of soluble fibre can modulate inflammatory responses in response to the production of short-chain fatty acids, in particular butyrate, which is involved in the activation of transcription factors which modulate the expression of genes encoding pro-inflammatory cytokines[146–148]. Dietary antioxidants, in particular vitamins C and E, are potent free radical scavengers where there is cross-sectional evidence showing an inverse association with pro-inflammatory cytokines[149,150]. Moreover, several systematic reviews have been published regarding the role of omega-3 polyunsaturated fatty acids (n-3 PUFA), a key lipid source within a MedDiet[151], on ameliorating inflammatory biomarkers in patients' chronic diseases[152,153]. In particular, the long-chain marine n-3 PUFA fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) partially inhibit a number of key aspects of inflammation including leucocyte chemotaxis, expression of adhesion molecules and leucocyte–endothelial adhesive interactions, production of eicosanoids and the up-regulation of pro-inflammatory cytokines, including TNF-α and IL-6[154,155]. Often interlinked, the proposed anti-inflammatory actions of marine n-3 PUFAs include altering the phospholipid fatty acid composition of cell membranes, inhibition of the pro-inflammatory transcription factor nuclear factor kappa B and activation of the anti-inflammatory transcription factor peroxisome proliferator-activated receptor γ[156].

Higher intakes of unsaturated fats (e.g., EVOO, nuts and fatty fish) have been associated with increased insulin sensitivity and improved beta cell function[157]. Specifically, bioactive compounds from EVOO (e.g., polyphenols) and marine n-3 PUFAs (e.g. EPA and DHA) act in the gastrointestinal tract to improve postprandial insulin release and sensitivity through increases in glucagon-like-peptide-1 (GLP1) expression from endocrine L-cells, which stimulates insulin secretion and inhibits glucagon secretion[157–159]. Moreover, EPA and DHA have also been shown to increase insulin sensitivity by altering the concentrations of adipokines including

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leptin, adiponectin, resistin and visfatin; increasing the expression of GLUT-4 and producing anti-inflammatory effects to increase glucose uptake[157]. Lastly, it is well documented that dietary flavonoids present in plant foods, in particular quercetin, hesperidin and anthocyanins possess anti-diabetic properties including enhancing the function of glucose transporters, reducing metabolic stress in mitochondria, improved beta cell functioning and attenuation of oxidative stress in response to inflammation in tissues including muscle, liver and adipose[160–162].

The proposed mechanisms whereby anti-inflammatory properties of a MedDiet and the influence on outcomes related to fertility, although largely unclear, have previously been reviewed by members of our team[163]. For example, excess ROS coupled with a low intake of dietary antioxidants results in oxidative stress. Chronic oxidative stress can cause lipid peroxidation of cell membranes and subsequent DNA damage in functioning cells of the reproductive system[164] which may help to explain how adherence to a MedDiet may enhances female fertility and IVF success rate. Moreover, a higher folate intake may increase the number of oocyte and embryo by facilitating DNA methylation[165]. With respect to menstrual parameters, pro-inflammatory mediators including PGF2-α and PGE2, which are associated with inflammation, play a role in dysmenorrhoea[166]. These prostaglandins cause pain by increasing contractions in the uterus and are also involved in enhancing vasoconstriction, thereby controlling local hypoxia and smooth muscle contraction and the production of anaerobic metabolites[166]. It has been postulated that marine n-3 PUFAs can ease menstrual pain and dysmenorrhoea by inhibiting arachidonic acid metabolism and suppressing the production of pro-inflammatory prostaglandins that are implicated in dysmenorrhoea[167] with its potential efficacy supported by findings from systematic reviews and meta-analyses[168,169].

A number of proposed mechanisms have been discussed to help explain the interplay between adherence to a MedDiet and risk of depression[170]. The most compelling related to the anti-inflammatory bioactive constituents of a MedDiet (e.g., carotenoids polyphenols and n-3 PUFAs) together with vitamins and trace minerals with antioxidant properties which can attenuate key biological mechanisms (e.g., oxidative stress and inflammation) related to depression[170]. Phenolic compounds in particular may play an important role due to their ability to protect neurones from oxidative stress and the interplay with nitric oxide to reduce inflammation and protect the vascular endothelium[171,172]. Other plausible mechanisms include normalising neurotransmitter production, HPA axis function and glucocorticoid receptor signalling, all of which are altered with depression[173,174]. Lastly, key dietary constituents of a MedDiet, namely nuts and legumes, which are rich in dietary fibre, unsaturated fatty acids and bioactive compounds (e.g., antioxidants and polyphenols), elicit a favourable prebiotic effect on the gut microbiota composition and the production of anti-inflammatory metabolites, such as butyrate[175].

Transferability and feasibility of a Mediterranean dietary pattern. Can it be followed in non-Mediterranean populations?

Whether the MedDiet, or at least principles of a MedDiet, can be followed in non-Mediterranean countries is up for debate and an emerging area of research. Nevertheless, due to its proposed health benefits, the translation of a MedDiet to non-Mediterranean populations is appealing and warrants ongoing research. Two previous feasibility studies conducted in Australia showed that participants generally felt confident in their capabilities of long-term adherence[176,177]. Similar findings have also been observed in the UK[178,179]. Furthermore, members of our team have previously reviewed the literature on the efficacy and adherence of a MedDiet used as a dietary intervention in clinical trials conducted in Australia against primary outcomes related to cardiometabolic risk factors, glycaemic control, cognition, hepatic steatosis and depressive symptomology[180]. Although long-term adherence was achievable, this was not without the inclusion of one-on-one and frequent counselling sessions provided by trained Dietitians, provision of educational resources and key food items consistent with a MedDiet (e.g., EVOO, legumes and nuts). As such, it remains unknown as to whether long-term adherence is possible, especially in non-Mediterranean populations, without adequate educational resources and support to help facilitate compliance[181]. Additionally, literature suggests a need for developing strategies aimed at enhancing skills related to goal-setting and self-efficacy for sustained dietary adherence[30,181–183]. A previous cross-sectional analysis of $n = 606$ Australian adults identified a number of important barriers towards adherence and uptake to a MedDiet, including knowledge, motivation, affordability, time and suitability[184]. In the context of PCOS, Moran et al.[185] used cross-sectional data from the Australian Longitudinal Study on Women's Health and reported that women with PCOS were more likely to consume a dietary pattern consistent with MedDiet principles, suggesting there is potential for acceptability of a MedDiet in PCOS. Nevertheless, feasibility and acceptability studies exploring the adherence to a MedDiet in PCOS are scant.

Future direction and conclusions

Given the inherit complexity in the pathophysiology of PCOS, the precise mechanisms related to how a MedDiet attenuates cardiometabolic, reproductive and psychological features of PCOS remains in an enigma. At present, evidence from clinical trials is limited but emerging[186]. Notably, ongoing studies, including those listed on clinical trial registries, investigating the efficacy of a MedDiet intervention on PCOS is scant. Our group is currently investigating the efficacy of a MedDiet intervention on hormonal, metabolic and anthropometric measures, without the need for caloric restriction, in women with PCOS and overweight or obesity[186]. Given that IR is a prominent clinical feature in the pathophysiology of PCOS, a dietary approach based on key principles of a MedDiet, without the need for caloric restriction, may indeed represent a novel dietary intervention for women with and without obesity. Importantly, results from the aforementioned study will provide preliminary evidence which can be further explored using longer-term and adequately powered multimodal clinical trials investigating the feasibility of a MedDiet intervention, coupled with lifestyle-related behaviour changes on outcomes pertinent in PCOS including cardiometabolic parameters, inflammatory markers, menstrual cyclicity, fertility and depressive symptoms. Of further importance, this work will also aim to identify the acceptability and feasibility of a MedDiet in women with PCOS. Given that there is limited literature on the feasibility and acceptability of a MedDiet intervention in women with PCOS, it is unknown whether there are unique barriers that would impede uptake and adherence within this population of women. Being able to identify and address potential barriers is an important step for

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informing effective and acceptable dietary interventions specific to clinical practice.

In conclusion, we have highlighted some observational evidence to support an inverse relationship between MedDiet adherence and PCOS features (namely IR and hyperandrogenemia). Nevertheless, well-designed clinical trials are needed to elucidate these findings. We have also explored the potential mechanistic benefits of the MedDiet on improving clinical features of PCOS which are likely related to the anti-inflammatory potential of the diet, reductions in oxidative stress and a higher intake of antioxidants. Although much of the proposed mechanisms are largely founded on individual anti-inflammatory bioactive constituents of a MedDiet (e.g., carotenoids, polyphenols and n-3 PUFAs), it is important to appreciate the important and complex synergistic relationship of nutrients and bioactive compounds within an existing dietary pattern. Whilst the current evidence is not yet sufficiently available to inform clinical practice, following a healthy dietary pattern, such as the MedDiet, to attenuate short and long-term symptoms associated with PCOS has little known adverse consequences and may aid in reducing the longer-term risks associated with cardiometabolic diseases and reproductive and psychological dysfunction in women with PCOS.

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