

Key points

- Untreated sleep disordered breathing in pregnancy poses risks to maternal and fetal wellbeing, but it is underdiagnosed.
- Careful approaches to screening could improve rates of diagnosis, but thresholds for and benefits of intervention are unclear.
- Clinical guidelines and screening programmes for sleep disordered breathing in pregnancy need to consider the potential harms of overdiagnosis and should involve shared decision making and careful monitoring of outcomes relevant to the individual.

Educational aims

- Explore current knowledge of the prevalence of sleep disordered breathing in the pregnant population.
- Explore the relationship between sleep disordered breathing and adverse outcomes.
- Understand the approaches to diagnosis and management of sleep disordered breathing in pregnancy.
- Explore issues around screening, underdiagnosis and overdiagnosis in the context of sleep disordered breathing in pregnancy.

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Review

Pregnant pause: should we screen for sleep disordered breathing in pregnancy?

Physiological and hormonal changes in pregnancy can contribute towards sleep disordered breathing in pregnant women (SDBP). When present, SDBP increases the risk of several adverse maternal and fetal outcomes independent of factors such as age, weight and pre-existing maternal comorbidities. SDBP is underdiagnosed and may be hard to recognise because the presentation can be difficult to differentiate from normal pregnancy and the severity may change over the course of gestation. Timely intervention seems likely to help reduce adverse outcomes, but the relative benefits of intervention are still unclear. The definition of what constitutes a sleep-related breathing "disorder" in pregnancy may be different to the general population and so traditional thresholds for intervention may not be relevant in pregnancy. Any modifications to the disease definition in this group, or implementation of more intensive screening, may result in overdiagnosis. Further research is needed to help clinicians evaluate the balance of benefits and harms in this process. Until this is clearer there is a strong imperative for shared decision making in screening and treatment decisions, and screening programmes should be monitored to assess whether improved outcomes can be achieved at the healthcare system level.

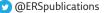
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Introduction

Several studies indicate that sleep disordered breathing in pregnancy (SDBP) carries increased maternal and fetal risks. Treatment of SDBP has the potential to reduce these risks but healthcare systems are poor at recognising it, and the condition is probably underdiagnosed. This review will discuss these issues in light of the most recent evidence relating to screening, prognosis and management of SDBP.

Sleep disordered breathing in pregnancy

Sleep disordered breathing (SDB) refers to a group of conditions characterised by dysfunctional respiration during sleep. Dysfunction may be central in origin, arising from abnormal ventilatory control, but is more commonly obstructive [1]. Obstructive events involve narrowing of the upper airway resulting in cessation of breathing (apnoea), reduction in airflow (hypopnoea) or an increase in airway resistance,



Untreated sleep disordered breathing in pregnancy poses risks to maternal and fetal wellbeing, but thresholds for and effectiveness of intervention are unclear. Clinicians should use shared decision making for screening and treatment decisions. http://ow.ly/N0oN30noWnx



resulting in arousal from sleep (respiratory effort related arousal). The presence of these respiratory events, in combination with symptoms such as snoring, gasping and daytime sleepiness are used to make a diagnosis of obstructive sleep apnoea (OSA). While most studies of SDB in pregnancy have focused on OSA, this review will use the broader term SDB to reflect the reality that many studies have used subjective definitions such as the presence of snoring, and that patients may present with a mixture of central and obstructive components. SDB is uncommon in women of childbearing age, but several factors can contribute towards it being more common in pregnant women, compared with their nonpregnant counterparts. During pregnancy, increases in blood volume, adipose tissue, oedema and rhinitis contribute to upper airway narrowing, while changes in thoracoabdominal compliance tend to elevate the diaphragm causing a reduction in functional residual capacity (FRC) [2]. These factors, along with increased respiratory drive due to hormonal changes, result in increased transpulmonary pressure during inspiration, and increasingly negative airway pressures [3]. These changes are to some extent dependent on the stage of pregnancy and so the severity of SDBP tends to increase from the first to the third trimester [2]. SDBP may therefore occur: 1) as a gestationally onset phenomenon; or 2) as a worsening in severity of a pre-existing abnormality, whether diagnosed or undiagnosed. There may be different diagnostic, prognostic and management implications of these two manifestations, but the distinction is rarely made in the literature, and can be difficult to determine

Prognostic consequences

In the general population untreated SDB has long been associated with an increased risk of cardiovascular and metabolic disease, cognitive impairment, depression, excessive daytime sleepiness and impaired quality of life [4]. Given that these risks may arise in part due to chronic untreated SDB, it is not clear that gestationalonset SDB, if spontaneously resolving post-partum, would pose the same risks. Instead, there has been growing concern that SDBP contributes to several adverse pregnancy-related outcomes including gestational diabetes mellitus (GDM), hypertensive disorders of pregnancy (HDP), pretern birth (PTB), fetal growth and birthweight, non-vaginal delivery and miscarriage [2, 5–7].

Many prognostic studies have failed to account for confounders such as body mass index (BMI) or maternal age, have used inconsistent indicators of SDB, or had inadequate power to assess rarer outcomes [8, 9]. Recently, several studies have gone some way to address these issues. A 2018 metaanalysis of 35 studies (n=56751837) separated those that used symptom-based markers of SDB (*i.e.* snoring) from those relying on objective diagnosis (OSA) [10]. OSA was associated with PTB (OR 1.75, 95% CI 1.21–2.55), but both snoring and OSA presentations were independently associated with increased risk of: GDM (snoring OR 2.14, 95% CI 1.63–2.81; OSA OR 1.71, 95% CI 1.23–2.38); pregnancy-induced hypertension (snoring OR 1.93, 95% CI 1.63–2.28; OSA OR 1.80, 95% CI 1.28–2.52); and pre-eclampsia (snoring OR 1.87, 95% CI 1.27–2.75; OSA OR 2.83, 95% CI 1.87–3.70).

Another recent systematic review and metaanalysis [11] examined SDBP as a risk factor for gestational age and birthweight at delivery, PTB, mode of delivery, cord pH, Apgar score, neonatal intensive care/special care unit, stillbirth, perinatal death, meconium at delivery, and wound complications. The initial analysis included 33 studies, but after excluding those that did not control for maternal obesity and age, a meta-analysis could only be carried out for three outcomes: SDBP was associated with PTB (OR 2.00, 95% CI 1.49–2.68), Caesarean birth (OR 1.73, 95% CI 1.52–1.98) and babies born small for gestational age, *i.e.* <10th percentile (OR 1.54, 95% CI 1.19–1.99).

A large retrospective, cross-sectional study based on International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes for OSA identified some associations with rarer pregnancyrelated complications [12]. The large sample size (n=1577632) allowed for comprehensive control for factors including obesity, pre-pregnancy hypertension and diabetes, age, ethnicity, parity, tobacco alcohol and drug use, rural/urban status, coronary heart disease, anaemia, hyperlipidaemia, hypothyroidism, and adrenal disorders. As well as identifying significant risks for GDM and HDP, this study hypothesises SDBP as a risk factor for pulmonary oedema, congestive heart failure, cardiomyopathy, postoperative wound complications, hysterectomy, length of hospital stay, and intensive care unit admission. Interestingly, this study found significant unadjusted odds ratios for SDB as a risk factor for poor fetal growth, but after controlling for confounders this relationship became nonsignificant. Studies relating SDBP to fetal growth are inconsistent, and several factors are probably involved. One study evaluated the effect of mild OSA on fetal outcomes independent of maternal risk factors by only including normotensive, non-obese, non-diabetic women [13]. Babies born to women with mild OSA (n=26) had a higher birthweight percentile (71 versus 57; p<0.01), were more likely to be large for gestational age (28% versus 8%; p=0.04) and were more likely to have a 1-min Apgar score ≤ 7 (23% versus 5%; p<0.01) than controls (n=129).

Plausible mechanisms exist to explain many of these poor outcomes, including sympathetic activation, inflammation, oxidative stress and endothelial dysfunction [7, 14]. Furthermore, the largest prospective analysis of objectively determined SDBP, to date, indicates an apparent exposure-response relationship between apnoeahypopnoea index (AHI) and pregnancy-related hypertension, as well as GDM [15]. Using home sleep apnoea testing (HSAT), this study identified that even mild OSA was associated with increased cardiometabolic risk. Although not fully understood, these mechanisms probably interact to cause impaired placental function, leading to poor fetal outcomes and increased intensity of medical intervention [9, 11].

Despite evidence linking SDB and insomnia to poor mental health status in the general population [16], there have been relatively few studies evaluating the link between SDBP and perinatal depression. One small cohort study found an association with poor or disordered sleep in pregnancy and maternal depression and anxiety [17]. Another study examined a group of women with a history of mood disorders (n=38) compared with a control group (n=45) [18]. This study used self-reported sleep and symptom assessments, including the Pittsburgh Sleep Quality Index (PSQI), Biological Rhythms Interview of Assessment in Neuropsychiatry and the Edinburgh Postnatal Depression Scale, carried out in the third trimester and between six and 12 weeks after birth. Both groups experienced worsening depressive symptoms as pregnancy progressed, and women with pre-existing mood disorders reported higher rates of disruption to biological rhythms and sleep, suggesting that disordered sleep contributes to severity of postnatal depression. There is also evidence that disordered sleep in pregnancy can impact infant wellbeing, such as increased risk of attention deficit hyperactivity disorder [19]. Treatment of SDB has been effective at reducing depressive symptoms in the general population [20, 21] and it seems reasonable to extrapolate this to pregnant women. However, there is as yet no clear evidence for this and further studies need to explore this relationship.

Prevalence

SDBP is associated with being older, having a higher BMI, being black, and with use of tobacco and drugs [12, 22, 23]. However, there is significant variation in estimates of overall prevalence. Few studies have used the "gold-standard" diagnostic modality of attended overnight polysomnography (PSG) [24] to assess prevalence. PSG involves measurement of respiratory and neurophysiological signals to stage sleep, identify respiratory events and identify sleep disturbance. Despite being the most sensitive measure of severity of SDB, the high cost and lack of access to PSG has led to a relaxation of American Academy of Sleep Medicine (AASM) clinical practice guidelines. Current recommendations allow a diagnosis to be made using respiratory HSAT devices in cases where comorbidities have been excluded [25]. These devices generally focus on

measurement of respiration and oxygen saturation, but lack electroencephalogram (EEG) measurement and so cannot detect arousal. Instead HSAT devices use measurement of respiration and oxygen saturation to produce an AHI. By failing to recognise arousal, HSAT is less able to detect milder SDB and may lead to false negative studies. The AASM guidelines also allow the use of pulsatile arterial tonometry (PAT) devices [25]. These devices use finger plethysmography sensors to detect changes in autonomic activity and can estimate the presence of EEG arousal. A small study in pregnant women (n=31) using the WatchPAT-200 device (Itamar Medical, Cesarea, Israel) gave a sensitivity and specificity of 0.88 and 0.87 for an AHI \geq 5 events \cdot h⁻¹, and 1.00 and 0.81 for a respiratory disturbance index ≥ 10 events $\cdot h^{-1}$, compared to unattended home PSG [26]. There are currently no guidelines on the most appropriate diagnostic modality in pregnancy, but given that SDBP typically exists at the milder end of the spectrum [22, 27] HSAT devices might not have adequate sensitivity and should be used cautiously.

In many healthcare systems cost is a major factor in decisions over diagnostic and screening modalities. Attended PSG requires an inpatient stay, as well as time-consuming setup, recording and analysis from skilled healthcare workers, making it impractical without pre-screening to identify women with a high pre-test probability. Many research studies have attempted to use screening questionnaires such as the STOP-Bang questionnaire, Berlin Questionnaire (BQ) or Epworth Sleepiness Score (ESS) to identify women at high risk of SDB. Using these measures, around 12% to 46% (first and third trimester, respectively) of women can screen positive [28]. These estimates need to be interpreted with caution however as questionnaires may not perform well in all stages of pregnancy [29]. A criticism of the STOP-Bang questionnaire when used in pregnancy is that two of the eight questions, referring to gender and age >50 years, are largely irrelevant, while another refers to feeling tired or fatigued in the day, which is a common feature of most pregnancies. A recent meta-analysis demonstrated a sensitivity and specificity of just 0.66 and 0.62 for the BQ, and 0.44 and 0.62 for the ESS when compared to PSG [30].

Compared to questionnaire surveys, prevalence estimates using objective measurement techniques tend to give quite varied estimates. The largest prospective study using HSAT measurements to date (n=3132) found OSA prevalence in early and mid-pregnancy to be 3.6% and 8.3%, respectively [15]. In a smaller sample (n=128) of "high-risk" women (BMI \geq 30 kg·m⁻², hypertension, pregestational diabetes, previous pre-eclampsia and/or a twin gestation), Facco *et al.* [31] found a much higher prevalence of between 30% and 50% (from early to late pregnancy). PAMIDI *et al.* [27] used more rigorous, but unattended home PSG monitoring to record an AHI >5 events·h⁻¹ in 66% of women (n=230), although the sample excluded women carrying babies predicted to be large for gestational age. PIEN *et al.* [22] carried out the largest study using "gold-standard" attended PSG. This study used a modest sample size (n=105) but used a stratified recruitment strategy to include individuals from a range of BMI ranges. First and third trimester OSA prevalence was estimated as being 8.4% and 24.4% respectively. While prevalence estimates based upon attended PSG arguably have better internal validity than HSAT studies, it is not clear whether estimates can be reliably transposed to other populations.

Underdiagnosis

Several studies which have interrogated diagnostic coding databases can offer an insight into the ability of healthcare systems to diagnose SDB at the population level. FELDER et al. [32] gueried a database of around 3 million pregnant women in California and identified OSA, based on ICD-9 codes, in around 0.05% of individuals. Similar studies using the US National Perinatal Information Center database [12] and the military hospitals "M2" database [33] found an OSA prevalence of 0.12% (n=1577632), and 0.087% (n=305001), respectively. These figures reflect the reality of clinical practice, in North America at least, but are clearly different to the findings of even the most modest objective screening studies discussed above. This disparity casts doubt on either the accuracy of the coding, the ability of healthcare systems to identify SDBP, or both, and suggests that SDBP is significantly underdiagnosed.

Given the significant body of evidence that there is an association between SDBP and adverse outcomes, it is important to understand why healthcare systems seem to be so poor at diagnosing it. Despite a high prevalence of SDB in the general population [34], recognition of the condition remains poor [35-37], particularly in populations with existing cardiometabolic disease [38, 39]. Recognition of SDB in nonpregnant women may be particularly problematic as the presentation is likely to be different compared to men. For example, women with SDB are more likely to report tiredness and sleep-onset insomnia, but less likely to report snoring or apnoeas [40]. As well as this sex-based difference, there is difficulty in defining what constitutes normal sleep and daytime sleepiness in pregnancy. A meta-analysis of 24 studies documenting sleep quality in pregnancy using PSQI found that 45.7% of pregnant women experienced "poor sleep" during pregnancy. A normal PSQI is generally considered to be <5, but the average score during pregnancy was 6.03, with scores increasing from the second to third trimester [41]. In another study using an internet-based questionnaire (n=2427), 100% of pregnant women reported frequent night-time awakenings and

most took daytime naps (78%) [42]. Furthermore, women diagnosed with third trimester OSA using attended PSG were not sleepier than controls, and the presence of daytime sleepiness does not reliably predict the presence of a sleep disorder [22]. These sleep-related features of pregnancy could be a result of a primary sleep disorder such as SDBP, restless leg syndrome or insomnia, all of which are well documented to increase in prevalence during pregnancy [43, 44]. They could also be secondary to pregnancy-related phenomena such as nausea, muscle cramps, shortness of breath, Braxton-Hicks contractions, fetal movements, nocturia, rhinitis, gastro-oesophageal reflux or raised body temperature.

Part of the reason for underdiagnosis is the apparent lack of a coherent approach to screening or diagnosis of SDBP. Questionnaire surveys of obstetric anaesthetists in North America [45] and the UK [46] revealed that most facilities do not have SDBP management guidelines, and many never screen for SDBP even when patients are deemed "high-risk". When screening does take place, the surveys indicate that the most common methods were ESS, BQ and STOP-Bang questionnaires, which as discussed have limited utility in this group. In another study, a survey of 776 women and 250 clinicians from the same hospital was used to evaluate the way in which SDB was assessed during prenatal care [47]. While 40% of recently post-partum women reported being asked by clinicians about sleep quality, fewer than 5% were asked about snoring or gasping, and only 1.8% were referred for a sleep evaluation. Clinicians corroborated this, with most reporting that they "almost never" asked about snoring or daytime sleepiness or made referrals to a sleep specialist. Referral rates seem particularly low given the risk factors in this group: around 32% of women in the sample snored, 22% were obese, 12% had a current or previous history of gestational hypertension, and 16% had a history of depression.

Another cause of low rates of diagnosis might be reluctance to undergo a diagnostic sleep study. In one study of 456 women identified as having a high likelihood of OSA based on questionnaire data, only 13% completed objective testing following referral [28]. The reason for this is not entirely clear as completion rates as high as 83% [22], 86% [48] and 81% [49] of consented women have been reported elsewhere. Reported reasons for non-completion included preterm labour, miscarriage, medically advised bed rest, lack of sleep centre capacity, lack of appropriate medical insurance and social obligations. Even when a diagnosis has been made, the perceived importance of SDB among pregnant women appears to be low. WILSON et al. [48] reported that <10% of women in their study with objectively measured SDB attended subsequent sleep physician appointments.

There is consensus that healthcare systems need to do more to improve diagnosis of SDBP

[14, 42, 44, 50]. The rationale for this is clear; if SDBP can be identified early on in pregnancy then it would serve as a potentially modifiable risk factor for a number of adverse outcomes [44]. But this opportunity needs to be balanced against the potential problems associated with overdiagnosis of disease. There is currently no evidence of overdiagnosis of SDBP; however, it is an important consideration in preventative medicine, and is a risk whenever diagnostic testing is carried out in the absence of symptoms [51]. In the context of pregnancy this understanding could be extended to include diagnostic testing where the symptoms are not distinguishable from those experienced in "normal" pregnancy. KALE and KORENSTEIN [51] identify some of the causative factors that are thought to contribute towards overdiagnosis. These include broadened disease definitions, technological advances, public health interventions, a culture of medicalisation and increased acceptance of riskreduction as a management strategy. Many of these factors are or could be present with regard to SDBP (table 1), and so clinicians and researchers have an obligation to take this into account when determining the most appropriate course of action.

Practical implications

There is a movement to revise diagnostic definitions of OSA in the general population in recognition of the existence of different clinical and pathophysiological phenotypes [52]. Existing evidence indicates that even mild SDBP or "snoring" conveys risk for several adverse outcomes and so clinicians and researchers should consider whether conventional thresholds for intervention need to be lowered. There are no specific guidelines for treatment of SDBP and the standard intervention for SDBP is assumed to be nocturnal continuous positive airway pressure (CPAP). Other options, such as surgery or mandibular devices, may not be appropriate due to concerns over safety or efficacy in pregnancy [50]. Small studies indicate that CPAP is safe, can be tolerated in pregnancy, and may improve pregnancy-induced hypertension, pre-eclampsia and GDM [50]. However, the evidence for this is not unequivocal [53], and larger scale randomised controlled trials are needed to fully understand the threshold at which intervention might be helpful.

An alternative treatment approach that requires further investigation is postural modification. Sleep in the supine position is associated with changes in lung volume and airway shape which may predispose airway collapse [54], and the supine position may exacerbate respiratory instability [55]. Some individuals exhibit sleep apnoea which is positionally dependent; with upper airway being more prone to collapse when supine. In the general population, sleep position trainers can be effective at reducing severity of OSA and are well tolerated over the short [56] and long term [57]. Positional OSA is more common in milder cases of OSA, potentially making it an appropriate intervention for pregnant women. This approach is consistent with current advice for pregnant women to sleep on their side. Although not evaluated specifically in the context of SDBP, an initial study has demonstrated that positional trainer devices are acceptable to pregnant women and can reduce supine sleep time [58]. Prospective randomised controlled studies are required to evaluate whether positional training devices can improve outcomes.

To minimise the potential consequences of overdiagnosis, clinicians must be able to evaluate the harms associated with any treatment. While CPAP may be safe, many find it very uncomfortable to use or fail to tolerate it [59]. Sleep disturbance is common in pregnancy, and comorbidities such as insomnia have an adverse effect on CPAP compliance [60], potentially limiting the utility of CPAP in this population. In addition, the CPAP setup and follow-up process may require several clinic visits. While treatment burden associated

Table 1	Potential	drivers	for overa	liagnosis	of SDBP

Category	Factor	Considerations in SDBP
Broadening disease definitions	Lowered diagnostic thresholds	Should snoring in pregnancy be considered a pathology?
Technology	Availability of testing	Is widespread testing more feasible with less- costly HSAT technologies compared with traditional gold-standard PSG?
Public health interventions	Widespread screening	Should prenatal healthcare systems introduce screening regimes to detect SDBP?
Culture of medical care	Value of diagnosis for its own sake	What are the labelling consequences of making a diagnosis of SDBP?
Clinician error	Overestimation of the benefit of therapy	Does "treatment" of SDBP improve maternal and fetal outcomes?
Adapted from [51].		

Self-evaluation questions

- 1. Which of the following statements is correct? SDBP is caused by ...
 - a) increased transpulmonary pressure during inspiration, caused by an elevated diaphragm, increased FRC and reduced ventilatory drive.
 - b) increased transpulmonary pressure during inspiration, caused by an elevated diaphragm, reduced FRC and increased ventilatory drive.
 - c) reduced transpulmonary pressure during inspiration, caused by an elevated diaphragm, reduced FRC and increased ventilatory drive.
 - d) reduced transpulmonary pressure during inspiration, caused by an elevated diaphragm, increased FRC and increased ventilatory drive.
- 2. Which of the following statements is correct? Current research suggests that ...
 - a) snoring alone is not associated with adverse outcomes such as GDM and pre-eclampsia.
 - b) both snoring and OSA are associated with adverse outcomes such as GDM and pre-eclampsia.
 - c) OSA alone is associated with adverse outcomes such as GDM and pre-eclampsia.
 - d) snoring alone is associated with adverse outcomes such as GDM and pre-eclampsia.
- 3. Which of the following statements is correct? Using gold-standard attended PSG the prevalence of OSA in pregnancy is around ...a) 8% in trimester one, rising to 24% in trimester three.
 - b) 4% in trimester one, rising to 8% in trimester three.
 - c) 12% in trimester one, rising to 46% in trimester three.
 - d) 4% in trimester one, rising to 46% in trimester three.
- Which of the following statements is correct? The potential harms associated with overdiagnosis might be mitigated by...
 - a) avoiding shared decision-making tools.
 - b) broadening the definition of SDBP to include snoring.
 - c) screening more pregnant women.
 - d) a better understanding of individual disease burden.

with CPAP might not compare to other chronic conditions, a "high-risk" pregnancy may require more intensive monitoring, and additional sleep clinic visits may be unaffordable, or impractical due to work or social care obligations. It is clear that treatment burden should be taken into account in the design of clinical services [61], and the same imperative holds for research programmes. Poor CPAP adherence has been a limitation to several studies investigating metabolic and cardiovascular outcomes, and work is underway to explore the feasibility of CPAP in the context of a large-scale randomised controlled trial in this population [62]. A better understanding of the perceptions of and preferences for other interventions would also be helpful in this context.

Pregnancy can be an emotive time and there is a need to understand the psychological effects of labelling with SDBP. A diagnosis of SDBP might increase the likelihood of a pregnancy being labelled as "high-risk", potentially limiting choice for women, for example by removing the opportunity for a home- or water-birth, or vaginal delivery. Some individuals may have a preference for risk reduction, even though the likelihood of a particular harm may be small. For others the psychological, financial or practical consequences of diagnosis or intervention may be of more concern. Therefore, when dealing with uncertainty clinicians should strive for shared decision-making approaches [63]. As well as reducing individual choice, there is the potential for the labelling of pregnant women with a condition to have a detrimental impact on maternal wellbeing. A recent study demonstrated that a perceived pregnancy risk has a significant negative effect on postnatal maternal well-being, even in the absence of objective risk [64]. Clinicians therefore need to empower individuals to make choices about screening for, and treatment of, SDBP in a way that avoids excessive anxiety [65]. In the absence of clear evidence that intervention can mediate risk, this is a difficult task, and researchers should work towards development of shared decisionmaking tools for use in this context.

Conclusion

SDBP is an underdiagnosed condition, but one which poses significant risks to maternal and fetal wellbeing, even at the milder end of the spectrum. Clearer clinical practice guidelines and more rigorous approaches to screening would probably improve rates of diagnosis, but a series of interrelated questions remain regarding when and how to screen, how to define a "disorder", and whether intervention is likely to produce a net benefit. In all cases the relative merits of screening and intervention depend to some extent on what harms are likely to cause the most concern to the individual. Researchers and clinicians need to consider ways to facilitate shared decision making, this includes exploring issues around treatment burden in this population. Any changes in disease definitions or thresholds for intervention need to consider the consequences of the change [66] and careful monitoring of relevant health outcomes is needed to evaluate the effect of new screening programmes.

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Conflict of interest

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Suggested answers

- 1. b. 2. b.
- 3. a.
- 4. d.

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