ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Diabetes in adolescence


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Executive summary and Recommendations

• Adolescence is the transitional phase of development between childhood and adulthood.
• Health care and emotional needs are distinctly different from younger children and older adults.
• It is important to understand the psychosocial and physiological development of adolescence and recognize that chronic diseases like diabetes have the potential to inhibit life experiences (E).
• Many adolescents experience a deterioration in metabolic control – attributable to the following:
  ◦ endocrine changes leading to increased insulin resistance (B),
  ◦ erratic meal and exercise patterns (C),
  ◦ poor adherence to treatment regimens (C),
  ◦ eating disorders (C), and
  ◦ hazardous and risk-taking behaviors (C/E).
• Increase in weight gain, particularly in females may be observed (C/E) provoking insulin omission to effect weight loss (C).
• It is essential to develop appropriate communication skills to facilitate teaching and education, and recognize the need for privacy and confidentiality for this age group (E).

• To-date, psychoeducation interventions have demonstrated modest benefit on psychological outcomes, but no effect on glycemic control (B/C).
• Recent randomized controlled trials of motivational interviewing have shown no benefit in either psychological measures or glycemic control (A).
• Developing a trusting and motivating relationship between health care professionals and the adolescent patient and maintaining continuity may result in better patient self-care (C/D).
• Maintaining parental support and involvement throughout adolescence is associated with better outcomes (C/E).
• Identifying the need for specialized psychological counseling may be helpful and can be facilitated using specific screening tools (E).
• Providing health education opportunities utilizing strategies that optimize self-care behavior and that involve open-ended discussion, problem solving, negotiated target setting, and the use of modern technology are recommended (B/E).
• Education and advice on a variety of health care matters, including employment, driving, alcohol, drugs, sexual health, and contraception, should be provided taking into account background cultural and religious influences (E).
• There should be no discrimination or stigma against people with diabetes in the workplace (E).
• Organize regular screening for diabetes complications (E).
• Encourage understanding of the need for and immediate benefits of improved metabolic control (E).
• Recognize the signs of mental health problems (depression, eating disorders, illicit drug usage, etc.) and the occasional need for psychiatric treatment (E).
• Recognize that young people have differing views on providing care for adolescents with diabetes should:
  • Understand the psychosocial and physiological needs are distinctly different from those of younger children or older adults. Adolescence involves training to become an independent adult and may result in failures and mistakes as well as success.
  In the context of type 1 diabetes many adolescents experience a deterioration in metabolic control (3–6) often attributable to erratic meal and exercise patterns (7, 8), poor adherence to treatment regimens (9–12), hazardous and risk-taking behaviors (1, 2, 13, 14), eating disorders (15–20) and endocrine changes associated with puberty, leading to greater insulin resistance (21).
  Changes in body habitus, particularly weight gain in females (3, 5, 22–25) may be unwanted diabetes-related side effects, sometimes associated with changes in the tempo of pubertal maturation (25, 26) provoking insulin omission to effect weight loss(12, 16, 18).
  It is therefore recommended (1, 2, 27–32) that those providing care for adolescents with diabetes should:
  • Understand the psychosocial and physiological development of adolescence (1, 2). This includes the recognition of the need for young people to shift (around the age of 10 yr onwards) from ‘concrete thinking’, with limited abstract capacity for understanding time perspectives or consequences of their actions, into adult cognitive capacity with a more realistic perspective of the future, which is achieved at a variable rate toward late adolescence (33).
  • Recognize that chronic conditions may inhibit some young people from exploring life, while others deliberately explore risk-taking behavior involving their diabetes care.
  • Develop communication skills [e.g., trusting, author-authoritative (not authoritarian), allowing adequate time, open questioning, patient-centered, observing non-verbal messages and confidentiality].
• Understand that attending to the developmental needs of young people may be just as important for quality of life as diabetes specific treatment (34, 35).
• Recognize the intensity of the changing social environment on behavior. Adolescents’ experience a strong need to fit in and be accepted outside the family – most importantly by peers.
• Acknowledge the emerging differences in lifestyle and changing needs of adolescents. Exploring various life styles is part of identity development and includes experimentation in many domains, most commonly in the company of peers.
• Identify the components of care unique to adolescents.
• Provide planned transition to adult care at the most appropriate time (35).

The weighted evidence base supporting these recommendations has been recently reviewed in both the Australian National Health and Medical Research Council guidelines (30) and UK National Institute of Clinical Excellence (NICE) guidelines (32).

**Identifying the components of care that are unique to adolescents**

Most aspects of optimal care of adolescents with diabetes have not been subjected to rigorous enquiry, hence results are conflicting. Extensive review of psychoeducational interventions has concluded that they may have modest benefit on psychological outcomes but not on glycemic control, although the methodological quality of most studies was moderate to poor (36, 37). Recent robustly designed randomized controlled trials of motivational interviewing interventions through training programs for pediatric diabetes teams appear to lead to no improvement in either psychosocial measures or hemoglobin A1c (HbAlc) levels (38).

Suggested care strategies might involve:

• Developing a trusting relationship between the adolescent and the diabetes care team, including through familiarity with staff and continuity in care (1, 32, 39). Adolescents report better self-care when health care professionals are motivating (1, 40).
• Helping the adolescent to clarify priorities and to set small achievable targets particularly where there is conflict between the needs of diabetes management and the adolescent’s social development and peer activities.
Cold Rigid Neglectful Indifferent
Non-empathic Authoritarian Unconcerned

Pediatric Diabetes

• Identifying and advising on which parenting styles
• Helping parents in their changing role from
• Helping the adolescent and parents to negotiate
• Recognizing the emerging maturity of the adolescent,
• Organizing regular screening for early signs of complications to encourage a practical understanding of the options available and the immediate, long-term and individual benefits of improved metabolic control (35, 41).
• Recognizing the emerging maturity of the adolescent, encouraging self-reliance and self-efficacy thus not only allowing consultations to be increasingly directed toward the adolescent but also retaining the trust and support of parents (42).
• Helping the adolescent and parents to negotiate new levels of parental involvement in diabetes care tasks (35).

Emerging independence is best pursued gradually:
• Helping parents in their changing role from full responsibility toward a gradual transition to cooperative care with the adolescent. This role change needs to be slow and gradual as continued parental support and involvement in day to day care is a strong determinant of improved clinical outcomes. This is based on evidence that parental support and involvement throughout adolescence is associated with better outcomes (C, E) (1, 42–48).
• Identifying and advising on which parenting styles are more likely to be successful than others [see Table 1 and (49)].

The authoritative parent sets age-appropriate demands respecting the maturity level and developmental needs, carefully explaining reasons for prohibiting certain behaviors and agreeing on strategies for behavior together with the young person in a respectful dialogue. The authoritative parent, however, does not bargain about serious matters and has a clear goal of what is important in the long run. Authoritative parents do not need much support but need medical information.

The authoritarian, rigid parent gives orders, puts his/her own ambitions first and does not consider needs and feelings of the child. The rigid and demanding families may need support to develop more adequate parenting individually or in groups.

The lenient, permissive parents are highly empathetic who seem to care too much about their children, over-identify themselves with the needs of their children and hate hurting them by getting into conflicts over routines.

The unconcerned, neglectful, and indifferent parents may have severe mental problems keeping them from understanding and helping their children. Neglectful parents require a careful social work-up to explore the roots of dysfunction.

• Having an index of suspicion for signs of mental health problems such as depression, eating disorders, ‘diabetes burnout’, illicit drug use, mental slowness, attention deficit hyperactivity disorder (ADHD), and neglectful or abusive family situations. Identifying the need for, and effectiveness of, specialized psychological counseling in some situations (50). The HEADS technique (acronym for Home, Education, Activities during spare time, Drugs and Sexual activities) is helpful when screening for psychosocial problems that might interfere with self-management (51).

• Providing health education, utilizing strategies that promote optimal health care behavior (see ISPAD Guideline Chapters on Psychological Issues and Education). Although there is consistent evidence that knowledge per se is predictive of better self-care and control this association is weak in adolescence (1). Thus, while it is essential that adolescents are provided with information about diabetes and its care, providing this information by conventional education alone may be insufficient to lead them to adopt optimal health care.

• Encouraging the adolescent to participate with parents and health care team members in making decisions about diabetes management.

• Enabling the adolescent to learn from mistakes without moral judgment.

• Offering a variety of educational opportunities including open-ended adolescent-orientated discussion and negotiation (52), discussing health-related quality of life issues (53), problem solving, target setting (50, 54), age-appropriate written materials, CDs/videos, text messaging (55), the use of the internet, social media, peer involvement, and group learning.

• Facilitated meetings with peers who have diabetes in order to receive advice, reflect and share experiences, and reduce feelings of isolation (56).

Sub-optimal metabolic control

The Diabetes Control and Complications Trial (DCCT) has unequivocally shown that intensive insulin therapy reduces risk of long-term vascular
complications, largely through improved HbA1c levels, and that better metabolic control in the early years of diabetes is also important in reducing this risk (57, 58). Metabolic control commonly deteriorates during adolescence, and this is partly due to physiological influences. However, the health care team should also consider the following:

- Socializing with peers is of utmost importance to most adolescents which often conflicts with their capacity to manage diabetes optimally.
- Adolescents with diabetes have the same needs for exploration as other young people but studies have shown that many of them are more vulnerable and subjected to more pressures to conform to peer norms (34, 35).
- Studies demonstrate slightly more involvement in health hazardous behavior in those with chronic conditions (14, 59).
- Adolescents may adopt non-demanding low risk metabolic control by deliberately adjusting their diabetes to a blood glucose level where they do not risk hypoglycemia or hyperglycemia/ketonemia and thus do not have their everyday life disturbed by diabetes.
- Some adolescents, particularly female, may manipulate insulin doses or dietary habits in order to reduce weight gain, which has the inevitable consequence of worse metabolic control and increased vascular complications risk (13).
- It may be helpful to negotiate from a cost-benefit stand-point to assist the young person to understand the short- and long-term costs of certain behaviors as well as the potential benefits.

Severe hypoglycemia

Severe hypoglycemia may be experienced during adolescence due to poor metabolic control, exacerbated by irregularities of lifestyle and risk-taking behaviour. In addition to the immediate effects on neurocognitive function, evidence shows an important link between severe hypoglycemia and preclinical atherosclerosis and acute and chronic cardiovascular events in later life (60, 61). This is relevant in the context of intensive insulin therapy that may increase the risk of severe hypoglycemia (62), although there is reassuring new evidence that hypoglycemia may be reduced in frequency by contemporary therapies (63) and careful attention to detailed education (64–66).

Specific concerns during adolescence include:

- Development of hypoglycemic unawareness or altered prodromal symptoms. An episode of severe hypoglycemia may lead to a period of altered awareness.
- Fears about hypoglycemia may be associated with poorer metabolic control (67).
- Confusion with alcohol intoxication.
- Confusion with illicit drug effects.
- Nocturnal or early morning episodes due to altered sleep patterns.
- The effect of hypoglycemia on driving.
- The effect of hypoglycemia on academic, sports, or work performance.

Young people should be encouraged to understand the benefits to them of better metabolic control. Advice should be given about hypoglycemia to enable adolescents to take positive measures in recognizing, managing, and preventing hypoglycemia (66, 68). Adolescents should be encouraged to inform friends about the risks, symptoms, and treatment of hypoglycemia during the altered routine of social engagements (1).

Alcohol, smoking, and drugs

Alcohol, tobacco, and illicit drug use is a serious concern in some communities during high school years (69). Notwithstanding the paucity of evidence of the variable contexts and type of alcohol consumption in adolescents with diabetes (70), advice on alcohol, smoking, and drugs should include:

- Encouragement to refrain from smoking and binge drinking, and advice on avoiding the dangers of drugs that may affect brain function or lead to dependence or addiction.
- Adopting a realistic advisory approach to alcohol rather than an absolute ban on medical grounds.
- Information on the effects of alcohol, particularly in young adolescents, on the liver by inhibiting gluconeogenesis with the possibility of either delayed severe hypoglycemia. This can variably combine with the carbohydrate content of the beverage to result in an unpredictable glycemic response (71).
- Methods of avoiding nocturnal hypoglycemia after drinking alcohol in the evening by ingesting carbohydrate while drinking, maintenance of good hydration, measuring blood glucose levels before bedtime, and having carbohydrate before sleep to minimize the risk of hypoglycemia.
- Ensuring that adolescents and their friends at parties and events where alcohol is consumed, are aware that hypoglycemia may occur when drinking alcohol without eating; that vomiting, particularly with omission of usual insulin, is dangerous and may be inhaled or lead to ketoacidosis; that hypoglycemia might be confused with intoxication and that it is important to check blood glucose levels before sleep.
Providing information for and education of colleagues or friends is increasingly important as the young person develops independence from the family, especially when living away from home at work, college, or university.

- Authoritative, but empathic, advice about smoking as an additional risk for the vascular complications of diabetes (C) (72, 73).
- Helping the adolescent who does smoke to stop by providing specific interventions that help with smoking cessation (nicotine-patch, cognitive-behavioral therapy, prescription drugs, etc.).
- Recognition that cannabis may alter eating habits (excess snacking during and loss of appetite after cannabis smoking) and may reduce motivation to maintain good metabolic control.
- Illicit drugs may alter brain function, increasing the risks of mistakes and mishaps with diabetes management.
- Acknowledgment that a risk reduction policy may be more realistic than an absolute ban on illicit drug experimentation.
- Introduce strategies for managing stress during adolescence other than medication, e.g., relaxation-training, exercise, psychological evaluation for anxiety or depression, hypnosis, etc.

Health care professionals should understand that educational messages which are motivating, problem solving, target setting, and which encourage adolescents toward developing their own strategies to avoid these problems are more successful than threats or inducing fear (E) (1, 35).

Driving

Hypoglycemia is the main factor which increases driving risk in people with diabetes (74), however, this risk is mitigated in an individual with glycemic awareness, stable metabolic control, and no visual disability to the extent where they are able to drive non-commercial vehicles (E) (75). Regulations vary in different countries. Studies have variably shown increased rates of driving accidents in drivers with type 1 diabetes (T1D) (75–77). Studies have also shown reductions in automobile accidents following specific hypoglycemia awareness training programs (C) (66–68).

The young person who plans to obtain a driving licence should be advised on the appropriate regulations and in particular:

- Prevention of hypoglycemia while driving (particularly if hypoglycemic unawareness is a problem) by blood glucose monitoring before starting to drive and appropriate food intake (75).
- Encouraging stable metabolic control (particularly avoidance of hypoglycemia) which may help determine whether a person with diabetes is eligible to hold a driving licence. Severe hypoglycemia in the preceding months causes many authorities to delay granting a licence.
- Regular visual acuity checks.

Employment

There should be no discrimination or stigma against people with diabetes in the workplace (77, 78). Most young people with diabetes should make good employees because of their ability to organize their lives and health care.

Advice on employment should include:

- Not concealing diabetes if asked about health and encouraging young people to inform potential employers about diabetes and how it is managed.
- The value of a good medical report from the diabetes care team may reassure employers that diabetes should not be a disadvantage in employment.
- Advice on those careers which may be unavailable to persons with diabetes, e.g., police, fire, armed and certain public services, driving large goods vehicles, or piloting airplanes. New technological developments may change these restrictions.
- Legal regulations vary between countries.

Reassurances to employers that young people with diabetes make excellent employees if they have shown mature self-care, self-discipline, and responsibility.

- Recommendations conclude that young people with diabetes should be prepared for the work place in the following ways:
  - Be responsible for self care including monitoring of blood glucose levels.
  - Be careful to avoid significant hypoglycemia.
  - Be candid about their diabetes to their employer.
  - Have a physician report to potential employers that supports the responsible diabetic young person.

Sexual health

Advice to young people with regards to sexual health will vary between different countries and cultures but would usually include (79):

- A non-judgmental approach to sexual activity.
- Advice where applicable on methods of avoiding pregnancy and sexually transmitted infections (STIs) for male as well as female adolescents.
Prevention of hypoglycemia during or after intercourse.
Advice on genital hygiene, vulvovaginal candidiasis, menstrual disorders, and STIs.
Pre-pregnancy counseling

Adolescent girls with diabetes should be aware of the importance of a planned pregnancy. Poor glycemic control around the time of conception increases the risks of congenital malformations, spontaneous abortion, and fetal death (C) (79–84). Pre-pregnancy counseling and education well in advance of the possibility of pregnancy is advisable with emphasis on:

- Ovulation is preserved, even when poor metabolic control and menstrual irregularities are present (85–87).
- The importance of good glycemic control before pregnancy, particularly the risks to the developing embryo and fetus.
- Understanding the importance of good control throughout pregnancy to avoid fetal macrosomia and neonatal hypoglycemia and also the avoidance of maternal hypoglycemia and ketoacidosis.
- Discussion with the young person and partner regarding the genetic risks of diabetes to their offspring.

Access to expert pregnancy management should include:

- Cooperative management by an obstetrician and physician with special experience in diabetes and pregnancy.
- Delivery of the baby in a hospital able to provide expert maternal, fetal, perinatal and neonatal care.
- Impotence

Males with long-standing diabetes may become impotent because of autonomic neuropathy (C) (88). Younger males may fear this complication and require expert counseling. Impotence in adolescence is rare and may be due to psychological reasons rather than diabetes itself.

Contraception

The diabetes care team should be sensitive to the religious and cultural influences affecting an individual’s choice of contraceptive method (79).

- When a female with diabetes becomes sexually active she should do so with knowledge of how to avoid an unplanned pregnancy and STIs (E) (11, 12).

A planned pregnancy in a person with diabetes in excellent metabolic control and in good health carries risks that are slightly higher than those in the general population, but not as elevated as previously reported (C) (89–91).

Barrier methods.

- Worldwide safe sex, STIs and HIV campaigns have made adolescents more aware of barrier methods, particularly condoms.
- Condoms offer the greatest protection against STDs to the whole genital tract (less against herpes), and substantial protection against pregnancy.
- Diaphragms are not recommended for the adolescent. Diaphragms are less effective contraception than the condom and do not protect against vaginal infection.
- Spermicidal gels probably increase the effectiveness of barrier methods.
- Coitus interruptus, a common practice among teenagers, is not recommended because it is associated with a high pregnancy rate.

Hormonal contraception and oral contraceptives.

- In the past, oral contraceptives (OCs) with 50μg of ethinyl estradiol (EE) were thought to have an adverse effect on metabolic control and lipid profiles and increase the risks of hypertension, cardiovascular, and thromboembolic diseases (C) (79, 92, 93). Nowadays, OCs with 50μg EE are rarely used.
- Newer OCs with a lower estrogen dose (≤35μg or less EE) and newer progestogens have not been demonstrated to be associated with detrimental effects on metabolic control, weight, or lipid profile (C) (79, 93–97).
- Young people with diabetes on OCs should be monitored regularly, particularly blood pressure, side effects such as headaches, mood changes, breast changes, and genital infections.
- Patients without micro- or macro-vascular complications and diabetes duration <20 yr may use any hormonal method (E) (98, 99).
- Patients with diabetes duration >20 yr, or having micro- or macro-vascular complications should avoid using OCs, but may use progestin only methods, intrauterine device (IUD), or barrier methods (E) (98, 99).
- Diabetes per se is not a risk factor of venous thromboembolism (C) (100).
- All women taking OCs, including patients with diabetes, should be educated on the signs of thromboembolic diseases. Educate about clinical signs of alert using the acronyms ACHES (abdominal pain, chest pain, headaches, eye, and severe leg pain).
Women with personal history of thrombotic disease should not use combined hormonal contraception (B) (98–101).
If acne or hirsutism are a problem, the use of an OC containing an anti-androgenic progestins may be helpful (C) (102–104).
Progesterone-only OCs may provide insufficient contraception for teenagers who are likely to forget the OCs.
Similar to other adolescents without diabetes, in some circumstances if there is the possibility of an unwanted pregnancy it may be beneficial to advise sexually active young people about the availability of the ‘morning after’ hormone pill. No special considerations for the adolescent with diabetes are recommended in this setting (E) (105).
Very obese patients should be aware of a decrease of contraceptive efficacy of hormonal contraception and higher risk of venous thromboembolism (C) (106).

Depot hormone injections.
Medroxyprogesterone injections have been associated with decreased bone mass gain, which may be especially detrimental for the adolescent with T1D (E).
No studies have evaluated combined hormonal monthly injection in patients with T1D, however, this method may be of use when the individual has an erratic life style and is at high risk of pregnancy (E).

Long acting reversible contraceptions.
Recently, long acting reversible contraceptions (LARCs), which include IUDs and the implantable rod, have been accepted as a first line contraceptive choice for nulliparous girls (E) (107, 108).
IUDs provide no protection against STIs, but are not associated with more episodes of STIs.

Study and examinations
Most adolescents will engage in a level of secondary and/or tertiary education that will require some form of formal assessment such as examinations. These may be significant life events in that they will to varying extent determine further educational and vocational opportunities. Advice as to how a student may deal with their diabetes to optimize academic performance is frequently sought. Many students are well aware of the cognitive effects of hypoglycemia (109, 110) and thus may choose to run their glucose levels higher than usual during exam times. They should however be counseled as to the equally negative cognitive impacts of hyperglycemia (111, 112). Glycemic responses to exams may vary with individual students stress responses, the type and length of the exam, and the time of day. Consequently students should undertake practice examinations in conditions that are as near as possible to those that will be experienced in the actual examination (i.e., same exam duration time, same time of the day, etc). Blood glucose levels should be checked immediately prior to and midway if a long exam (such as 3 h). Adjustments to insulin regimens and/or diet can then be made accordingly so as to maintain euglycemia during the exam. As a general principle over the course of the academic year, exercise should be encouraged to reduce stress, improve physical fitness, improve sleep patterns, and improve cognitive performance (113).

Transition from pediatric to adult services
The concept of transition implies a ‘planned, purposeful movement of the adolescent or young adult with a chronic disease from a child (and family) centered to an adult orientated health care system’ (2). The transition from a pediatric to an adult orientated service should not involve a sudden unanticipated transfer but an organized process of preparation and adaptation. The process should be a component of a high quality, multi-disciplinary diabetes service (including the use of linked databases) and must involve both teams of carers, an understanding of the two different systems of care and the differing expectations of those providing and those receiving care.
The appropriate age for transfer from a pediatric or adolescent service to adult care varies according to the maturity of the adolescent, the availability of appropriate services for the young person in an adult clinic and may be determined by hospital and clinic facilities and regulations. Young people have differing views on the appropriate age of transfer (32–35, 114, 115). Recent developmental psychology theory suggests that the transition should be toward emerging adulthood and not to young adult status (116). There is a potential danger that young people become lost in the transition process and cease regular attendance at the specialized service (C) (117). This is likely to be associated with poor adherence to treatment with increased risk of acute (12) and long-term complications of diabetes including increased mortality (C) (118). As no controlled studies have been performed the following recommendations are nearly all based on expert consensus opinion (E) (119).
For successful transition to an adult service, the following steps should be considered:

- Identifying an adult service able to provide for the needs of young adults with diabetes.
Cameron et al.

- Providing a joint adolescent or young adult clinic with members of both professional teams working together to facilitate the transition process for both adolescents and their parents.
- Liaison between the pediatric and adult services. Ideally this should involve identifying a specific person in the service (a ‘key worker’) who is able to move between both services to help the transition of the young person into the adult service. There is evidence that the appointment of a specialist nurse for adolescence has been successful in this role (C) (120). If such a person is not available, one of the pediatric staff should take responsibility for liaison with the adult service and both groups must have understanding of the services involved.
- Discussion with the adolescent and parent well in advance as to the best time for transfer, based on not only their own preference and readiness, but also on the availability of services and, in some countries, health care insurance requirements. It is preferable to have flexibility about age of transition as family circumstances and an adolescent’s psychosocial maturity differ widely.
- Development of clear, documented plans for transition services, and provision of a clinical summary of the young person’s medical history including indices of control, the results of complication screening and information on any comorbidities that may impact on how the person is managed medically.
- Good communication, including a written patient care pathway and protocol (30–32, 35), to facilitate understanding between all services providing care for the young person, particularly all members of the two diabetes teams and including, where available, primary care physicians and community nursing staff.
- Ensuring that there is no significant gap in care between leaving the pediatric service and entering the adult service and that the young person is not lost to follow-up care (35). This may occur if the young person fails to make or keep an appointment, or feels uncomfortable in the new service and loses touch with a specific named team member.
- The diabetes transition service should have mechanisms in place, including a database and a named professional, to identify and locate all young people who fail to attend follow-up consultations.

The adult service should be strongly encouraged to ensure long-term follow-up and outcome measurements of those who have developed diabetes as children and adolescents as many studies show poor glycaemic control and longer term morbidities (C) (121, 122).

To date there have been very few robust studies investigating best models of transition to adult care services (123). Several trials are currently underway attempting to address this lack of evidence base (124).

Conflicts of interest

The authors have declared no conflicts of interest.

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