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RESEARCH REVIEW

Co-occurring medical conditions in adults with Down syndrome: A systematic review toward the development of health care guidelines. Part II

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Abstract

Adults with Down syndrome (DS) represent a unique population who are in need of clinical guidelines to address their medical care. Many of these conditions are of public health importance with the potential to develop screening recommendations to improve clinical care for this population. Our workgroup previously identified and prioritized co-occurring medical conditions in adults with DS. In this study, we again performed detailed literature searches on an additional six medical conditions of clinical importance. A series of key questions (KQ) were formulated a priori to guide the literature search strategy. Our KQs focused on disease prevalence, severity, risk-factors, methodologies for screening/evaluation, impact on morbidity, and potential costs/benefits. The available evidence was extracted, evaluated and graded on quality. The number of participants and the design of clinical studies varied by condition and were often inadequate for answering most of the KQ. Based upon our review, we provide a summary of the findings on hip dysplasia, menopause, acquired cardiac valve disease, type 2 diabetes mellitus, hematologic disorders, and dysphagia. Minimal evidence demonstrates significant gaps in our clinical knowledge that compromises clinical decision-making and management of these medically complex individuals. The creation of evidence-based clinical guidance for this population will not be possible until these gaps are addressed.

KEYWORDS

adult health conditions, clinical practice guidelines, Down syndrome, evidence-based medicine, literature review, trisomy 21

1 | INTRODUCTION

Although the life expectancy of persons with Down syndrome (DS) has increased dramatically in the last half century and now approaches an average of 60 years in many developed countries, consensus-based guidelines for adults with DS over 21 years do not exist (Bittles and Glasson 2004; Glasson et al. 2002). Given this absence of clinical guidance there is concern among health professionals, self-advocates, and caregivers that the medical and mental health needs of this adult population continues to remain underserved (Capone et al. 2018; Carfi et al. 2015; Jensen et al. 2013). Such questions have taken on greater importance as adults with DS are living

Authors listed are in the order of contribution.

longer (Presson et al. 2013) and typically experience an increased burden of chronic medical conditions associated with high morbidity or mortality, some of which may be preventable (Bittles et al. 2007; Esbensen 2010; Glasson et al. 2014; Tenenbaum et al. 2012).

Consensus-derived health supervision guidance for children with DS (birth-21 years) have existed since 1994 (AAP 1994) and continue to be revised on a regular basis based on new or emerging evidence (AAP 2011). There does exist a growing literature in peer-reviewed medical journals addressing screening and/or evaluation for many of the co-occurring medical conditions seen in adults with DS (Capone et al. 2018; Galley 2005; Jensen and Bulova 2014; Malt et al. 2013; Smith 2001; Steingass et al. 2011; Wilson et al. 2015). For the past decade, the Down Syndrome Medical Interest Group in the U.S.A. (DSMIG-USA) has met annually to focus on health care and related topics at their annual symposium, and since 2014 adult health has received special priority (DSMIG-USA 2019). In 2018, a systematic review was published by our workgroup formally reviewing seven high priority medical conditions (congenital heart disease, thyroid disease, cervical spine disease, hearing impairment, overweight/obesity, sleep apnea, and osteopenia/osteoporosis) that often co-occur in adults with DS. This effort serves as both a step toward health care guidelines and in an effort to shape a future research agenda (Capone et al. 2018).

The goal of this review was to build on previous study, with a focus on six additional medical conditions including: hip dysplasia, menopause, acquired cardiac valve disease, type 2 diabetes mellitus, hematologic disorders, and dysphagia. These topics were based on recommendations from the work group to focus on areas that were commonly of clinical concern (see Methods). As described in part I of our previous review, we used the National Library of Medicine (NLM) database PubMed (MEDLINE) to identify review articles from peer-reviewed journals that discuss co-occurring medical conditions and their relative frequency in adults with DS (Capone et al. 2018). Next, we identified original research articles that addressed the prevalence and severity of the conditions and the methodologies used for screening and evaluation. The quality of that evidence was reviewed and implications for the development of practice guidelines were formulated. Finally, critical areas of deficit in clinical knowledge were identified and implications for future research discussed.

A series of key questions were formulated and designed to inform our understanding about the diagnosis and management of these common conditions to further inform clinical decision making.

1 Is the prevalence of (condition) in adults with DS known?
2 Is the severity of (condition) in adults with DS known?
3 Among adults with DS can those at ultra-high risk (for condition) be identified?
4 What are the screening or evaluation methods utilized?
5 Does screening or evaluation lead to reduced morbidity or mortality?
6 What are the financial costs, potential benefits or harms of screening or evaluation?

2 | MATERIALS AND METHODS

2.1 | Survey of resources on health conditions

As previously described in our workgroup's first publication, using the National Library of Medicine (NLM) PubMed database (NCBI 1943–2018) a survey of review articles that discussed the co-occurrence of medical conditions in adults with DS was completed (Capone et al. 2018; Henderson et al. 2007; Jensen et al. 2013; Jones 2009; Maatta et al. 2011; Real de Asua et al. 2015; van Allen et al. 1999; Van Buggenhout et al. 1999). Additional sources of reference not indexed in PubMed included books and book chapters, (Chicoine and McGuire 2010; Pueschel 2006; Pueschel and Pueschel 1992; Rubin and Dwyer 1989) guidance documents prepared for health providers (Cohen and Group 1999; Sullivan et al. 2006; Van Cleve et al. 2006), several journal articles (Kerins et al. 2008; Prasher 1994), and websites (Forster-Gibson and Berg 2011).

2.2 | Topic selection

Seven conditions, congenital heart disease, thyroid disease, cervical spine disease, hearing impairment, overweight/obesity, sleep apnea, and osteopenia/osteoporosis were addressed in our first publication (Capone et al. 2018). In this installment, we identified six additional conditions that are frequently the focus of clinical concern: hip dysplasia, menopause, acquired cardiac valve disease (without CHD), type 2 diabetes mellitus, hematologic disorders, and dysphagia. Three of these topics (menopause, cardiac valve disease, and diabetes) were identified as priority topics in our initial search, but not reviewed in the first manuscript. Three additional topics, (hip dysplasia, dysphagia, and hematologic disorders) are commonly encountered in clinical practice but often overlooked in medical reviews on adults with DS. They were included in this review based upon recommendations by the workgroup itself. Additional medical topics will continue to be reviewed by our workgroup given the availability of published literature to support this endeavor.

2.3 | PubMed literature search

The topical literature searches were conducted between 2017 and 2018 using PubMed to identify original clinical research manuscripts. We used the Medical Subject Headings (MeSH; the NLM controlled vocabulary thesaurus for indexing) to capture related entry terminology in our searches. For example, the MeSH term “Down syndrome” included the search entry terms: Downs syndrome, Down's syndrome, Mongolism, Trisomy 21, and Partial Trisomy 21.

The MESH term “Down syndrome” was combined with one or more main heading MESH terms to identify all of the available articles on that topic (unfiltered search). Then, the limiters *Human* and *≥19 years* were applied to narrow the scope (filtered search). Abstracts were reviewed and excluded according to their relevance as

TABLE 1 PubMed search terms, excluded and included articles by condition

Condition	MeSH search term(s)	Unfiltered search hits	Filtered search hits	Excluded from review	Included in review
Hip dysplasia	Hip dislocation (hip dysplasia, hip displacement)	251	213	209	4
Menopause	Menopause	31	25	20	5
Cardiac valve disease	Heart valve disease, (mitral valve, aortic valve, pulmonic valve) insufficiency; stenosis; prolapse	1,482	589	581	8
Type II DM	Diabetes	734	90	84	6
Hematology	Anemia	175	56	50	6
Dysphagia	Dysphagia, deglutition, swallowing	155	41	36	5

pertaining to the KQs (see below). A majority of articles were excluded at this stage. Whenever an abstract made mention of any KQ, or there was doubt, the full article was procured. The methods and results sections were reviewed to determine which articles met inclusion or exclusion criteria. A single reviewer from our group was chosen to conduct the literature searches, data review and extraction process. All data was reexamined for accuracy by the lead authors. See Table 1 for results of PubMed searches.

2.4 | Inclusion criteria

Study sample includes those ≥19 years (may also include younger subjects who were then removed from data analysis), data addresses at minimum one KQ, supporting data is original (not previously published), any case series or cohort that included >5 participants, any using a case–control research design or a randomized clinical trial.

2.5 | Exclusion criteria

Study sample includes those ≤19 years (exclusively), data does not address at least one KQ, article does not explicitly provide a methodology, the article does not provide original supporting data or uses data that was previously published.

2.6 | Data extraction

Using only the PubMed articles meeting inclusion, data pertaining to KQ was extracted from the abstract, methods, and results sections and entered into a preformatted Excel data template for analysis. See Table 2 for a summary of the articles used for the data extraction.

2.7 | Evidence ratings by condition

Next a critical appraisal of each of the included articles was performed to determine the type of research design used, method of subject ascertainment, total number of study participants, source of control subjects, and the extent of internal and external validity. The grading of *internal validity* considers study design factors such as ascertainment and selection bias, test procedures, and consideration of confounding variables. Using a research design hierarchy studies are graded as poor, fair, or good according to a set of predefined minimal criteria. Criteria differ based upon the type of study being considered (systematic review, case–control, randomized controlled trial, or cohort study). The grading of *external validity* considers the generalizability of findings to a broader, more representative population based upon attributes of the study population, the clinical setting, and qualifications of the personnel conducting the study (USPSTF 2008). See Appendix VII in the USPSTF report for criteria on research design hierarchy, and the grading system used for scoring internal and external validity. See Table 3 for summary of evidence ratings.

3 | RESULTS

3.1 | Hip dysplasia

Of the four articles reviewed, all were small, cross-sectional, and cohort studies (III) (Bennet et al. 1982; Hresko et al. 1993; Roberts et al. 1980; Shaw and Beals 1992). The total number of patients with DS was small (N = 273) and no control subjects were utilized. One study (Bennet et al. 1982) included a single child of under 10 years, another study included subjects from 10 to 70 years. Articles were published between 1982 and 1993, and addressed KQ 1–3, Table 2.

Plain radiographs were used to diagnose hip dysplasia. The prevalence of hip dysplasia across these studies was between 5 and 20%. In children with DS, the estimated prevalence is 1.3–7%, with a peak incidence of frank and recurrent dislocation between 2 and 10 years of age (Abousamra et al. 2016; Kelley and Wedge 2013). Excessive joint mobility and other markers of ligamentous laxity were thought to indicate increased risk. In the series of 18 patients followed for 9 years, two of seven patients with disease at baseline showed progression. Among participants with normal findings at baseline, four out of 11 went on to develop disease. In one study, those with normal hips were more likely to be community ambulators, while those with dysplasia were less likely (Hresko et al. 1993).

TABLE 2 Articles used for data extraction by condition

	Publications (*N*) dates	Subjects (*N*)	Age range[a]	Source of subjects	Methods	Study design
Hip dysplasia	(4) 1982–1993	DS = 273 CTR = 0	10–70 years	Community and residential facility	Plain films, X-rays	Cohort (4)
Menopause	(5) 1997–2010	DS = 651 CTR = 187	21–70 years	Community and residential facility	Behavioral scales, cognitive assessments, record review, structured/semi-structured interviews	Case–control (1), Cohort (4)
Cardiac valve disease	(8) 1986–2010	DS = 619 CTR = 122	9–63 years	Outpatient clinic and residential facility	Cardiac exam, echocardiogram	Case–control (1), Cohort (4), Case series (3)
Type II DM	(6) 1998–2015	DS = 6,714 CTR = 19,276	17–68 years	Outpatient DS clinic, diabetes unit, residential facility, national database	Record review, survey	Case–control (3), cohort (2), case series (1)
Hematology	(6) 1988–2015	DS = 330 CTR = 27	17–66 years	Outpatient clinic, residential facility, day program	CBC	Case–control (2), Cohort (2), Case series (2)
Dysphagia	(5) 2001–2016	DS = 287 CTR = 378	16–68 years	Outpatient clinics, residential facility, daycare centers	Water swallow test, observation, esophogram, manometry	Case–control (3), Cohort (2)

Abbreviations: CTR, participants without Down syndrome (may include typical individuals or those with intellectual disability); DS, participants with Down syndrome.
[a]Age range—those participants <19 years were removed from data analysis.

Two studies received *internal validity ratings* of fair and two of good. Two studies were given *external validity* ratings of poor and two of fair, Table 3. Those receiving a rating of poor generally reflected ascertainment of subjects solely from a long-term institutional setting.

3.2 | Menopause

Of the five articles reviewed, one was a case–control (Schupf et al. 1997) and four were cohort studies (II-2) (Coppus et al. 2010; Cosgrave et al. 1999; Schupf et al. 2003; Seltzer et al. 2001). The number of subjects with DS (*N* = 651) was modestly large and the number of controls (*N* = 187) was small. The age range of participants was 21–70 years. Articles were published between 1997 and 2010, and addressed KQs 1–3, Table 2.

Behavioral scales, cognitive assessment, record review, structured and semi-structured interviews were used to evaluate menopause experience in women with DS. The mean age of menopause was approximately 2 years earlier in women with DS compared to the general population of women and ranged from 44.7 to 47.1 years, and the median age range of menopause was 47.1–49.3 years (Schupf et al. 2003). Earlier age at menopause was associated with an increased risk of dementia in three studies (Coppus et al. 2010; Cosgrave et al. 1999; Schupf et al. 2003) and increased mortality in one study (Coppus et al. 2010). The impact of co-occurring thyroid disease was considered in each of the studies and obesity was considered in two. Three studies received *internal validity ratings* of fair and two of good. One study received an *external validity* rating of fair and four were good, Table 3.

3.3 | Acquired cardiac valve disease

Six of the eight studies on cardiac valve disease (CVD) were done using adult DS cohorts without controls (III) (Barnett et al. 1988; Geggel et al. 1993; Goldhaber et al. 1986, 1987; Pueschel and Werner 1994; Vis et al. 2010). Two studies utilized a case–control design (Goldhaber et al. 1988; Hamada et al. 1998). A single study employed prospective cardiac screening in a subset of participants (Vis et al. 2010). Participants were ascertained through convenience samples including, medical clinics and residential facilities. The cumulative number of subjects with DS (*N* = 619) was modestly large and control subjects without known cardiac disease (*N* = 122) was small. Participants ranged in age from 9 to 63 years. All articles were published between 1986 and 2010, and addressed KQs 1–2, Table 2.

The data reviewed included standard measures of cardiac function—cardiac exam, electrocardiogram (EKG), and echocardiography (ECHO). The subjects studied had no known history of congenital heart disease (CHD). Non-cardiac medical co-morbidities were not considered in any of the studies. Three studies received an *internal validity* rating of fair and five were rated as good. The *external validity* or generalizability of the findings received a rating of fair in five studies and good in three, Table 3.

3.4 | Type 2 diabetes mellitus (T2DM)

Of the six articles reviewed, one used a case–control design (II-2) (Alexander et al. 2016), two used a cohort (II-2) (Real de Asua et al. 2014a, 2014b), and three were case series (III) (Fulcher

TABLE 3 Evidence ratings by condition

	Number of key Qs addressed	Research design hierarchy[a]	Internal validity category	External validity category
Hip dysplasia	3	III	Fair (2), Good (2)	Poor (2), Fair (2)
Menopause	3	II	Fair (3), Good (2)	Fair (1), Good (4)
Cardiac valves	2	III	Fair (3), Good (5)	Fair (5), Good (3)
Type II DM	3	II–III	Poor (1), Fair (2), Good (3)	Poor (1), Fair (4), Good (1)
Hematology	2	II–III	Poor (2) Fair (2), Good (2)	Poor (2) Fair (3), Good (1)
Dysphagia	2	II–III	Fair (2), Poor (3)	Poor (3), Fair (2)

Abbreviations: I, Properly powered and conducted randomized controlled trial (RCT); well conducted systematic review or meta-analysis of homogeneous RCTs; II-1, Well-designed controlled trial without randomization; II-2, Well-designed cohort or case–control analytic study; II-3, Multiple time series with or without the intervention; dramatic results from uncontrolled experiments; III, Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.
[a]Research design hierarchy (from USPSTF 2008,p. 36).

et al. 1998; Ohyama et al. 2000; Taggart et al. 2013). In the case–control studies, the number of participants with DS (*N* = 6,714) and healthy controls (*N* = 19,276) were both large. Subjects ranged in age from 17 to 68 years. All articles were published between 1998 and 2015, and addressed KQs 1–3, Table 2.

Most participants were from a single study (Alexander et al. 2016). Subjects in two studies were presumed to substantially overlap based on authorship, timing and description of methods and were only counted once toward total subject number (Real de Asua et al. 2014a, 2014b). Subjects were ascertained from a longitudinal database (96%), outpatient clinic (1%), anonymous survey (1%), a residential living facility (1%), and a diabetes unit (1%). Two studies included laboratory evaluation (Real de Asua et al. 2014a, 2014b); two were from a survey-based dataset (Alexander et al. 2016; Taggart et al. 2013); and two involved retrospective chart review (Fulcher et al. 1998; Ohyama et al. 2000). We assigned *interval validity* ratings of good to three of the articles, fair to two and poor to one of the studies based upon design considerations. One study received *external validity* rating of good, another four were fair while one was rated as poor Table 3.

Various clinical measures were reported including weight, height, BMI, age, waist circumference, waist-to-height ratio, total body fat percentage; and laboratory evaluation included fasting blood glucose, insulin and HbA1C, creatinine, TSH, free T4, cholesterol, HDL, LDL, and triglyceride levels (Real de Asua et al. 2014a, 2014b).

Comorbidities assessed included, family history of early cardiovascular events, presence of arterial hypertension, dyslipidemia, diabetes mellitus, smoking, other conditions (thyroid disorders, obstructive sleep apnea, and Alzheimer's disease), relevant medications (including anti-hypertensive agents, lipid lowering agents, anti-diabetic drugs, anxiolytics, anti-depressants, anti-psychotics, anti-epileptics, non-steroidal anti-inflammatory drugs, levothyroxine, corticosteroids, vitamin B or D supplements, and oral contraceptives/estrogen replacement therapy), and dietary fat, fruit, and fiber intake (Real de Asua et al. 2014a, 2014b). Only a single study focused on the risk for long-term consequences (retinopathy) in those with DS and diabetes (Fulcher et al. 1998).

3.5 | Hematologic disease

Of the six articles reviewed, two used a case–control design (II-2) (Akin 1988; Vergnes et al. 1992), three were cohort studies (II-2) (McLean et al. 2009; Shabayek 2004; Wachtel and Pueschel 1991) and one was a case series (III) (Real de Asua et al. 2015). From the case–control studies, one used participants with intellectual disability at the same educational facility as controls (Akin 1988) while another used an unspecified control group (Vergnes et al. 1992). The cumulative number of participants with DS was small (*N* = 330) who were ascertained from outpatient clinics (44%), educational facilities (32%), a hospital (18%), and a hematology service (3%). Only two studies utilized control subjects (*N* = 27). All articles were published between 1988 and 2015, and addressed KQs 1–2, Table 2.

Four studies included prospective laboratory evaluation (Akin 1988; Shabayek 2004; Vergnes et al. 1992; Wachtel and Pueschel 1991) while two were retrospective (McLean et al. 2009; Real de Asua et al. 2015). Laboratory evaluations included hemoglobin values (Shabayek 2004), complete blood count (CBC) and related investigations in some studies such as serum vitamin B12 or folate levels (Akin 1988; Real de Asua et al. 2015; Wachtel and Pueschel 1991), iron studies (Wachtel and Pueschel 1991), TSH, freeT4, lipid profile, uric acid, and 25-OH-vitamin D levels (Real de Asua et al. 2015). The comorbidities assessed in specific studies included cardiac disease (McLean et al. 2009; Real de Asua et al. 2015) and thyroid disease (Akin 1988; Real de Asua et al. 2015.

The frequency of *anemia* in DS adults as reported in two different studies are quite discrepant at two of 61 (3%) (Wachtel and Pueschel 1991) and 76 of 89 (85%) (Shabayek 2004). These two studies differed in location, population, age of individuals sampled and normative laboratory cut-off values. Some studies showed "no difference" in hemoglobin compared to controls (Akin 1988; Real de Asua et al. 2015). One study analyzed the frequency of anemia by severity with "moderate anemia" observed in 28.6% of the females and 16.1% of the males with DS (Shabayek 2004). The effect of age demonstrated an increasing prevalence of anemia from childhood to early adulthood; as age-specific (19–24 years) hemoglobin values differed by sex with males = 12.5 ± 0.6 and females = 10.9 ± 1.8

TABLE 4 Hematologic laboratory parameters (Mean ± *SD*)

	Akin (Akin 1988)	Wachtel (Wachtel and Pueschel 1991)	Vergnes (Vergnes et al. 1992)	McLean (McLean, McHale, and Enright 2009)	Real de Asua (Real de Asua et al. 2015)
RBC (10^{12}/L)			4.525 ± 0.347		
Hemoglobin (g/dl)		14.8 ± 1.2	14.35 ± 1.14	15.1 ± 2.2	15.2 ± 1.6
Hematocrit (%)		44.5 ± 3.7			
MCV (mm^3)	101	99.1 ± 3.9	94.72 ± 4.38	98.76 ± 5.31	91 ± 11
Leukocytes (×10E3/mm^3)	8.1		6.02 ± 1.7	4.64 ± 1.85	5.8 ± 1.8
Neutrophils			2.92 ± 1.30		
Lymphocytes			2.48 ± 0.78		
Platelets (×10E3/mm^3)				196 ± 71	232 ± 56
Folic acid (ng/ml)		358 ± 151			7.7 ± 3.6
Vitamin B12 (pg/ml)		516.5 ± 221.6			441 ± 156
Fe saturation (%)		29.49 ± 6.7			

(Shabayek 2004). Anemia in DS was also higher in those from lower socioeconomic strata compared to middle and high (Shabayek 2004).

The frequency of *macrocytosis* as reported in one small study was seven of nine (78%) (McLean et al. 2009). A previous report showed that red blood cell (RBC) folate and serum vitamin B12 deficiencies were not related to the macrocytosis (Wachtel and Pueschel 1991). Laboratory values available from each study are summarized; but many did not provide normative values preventing us from calculating a prevalence, Table 4.

A single very small case series reported the frequency of *neutropenia* as (22%) and erythrocytosis (22%) in two of nine participants (McLean et al. 2009). "Benign" neutropenia is a common finding in adults with DS but has not received much research attention.

We assigned *interval validity* ratings of good to 2, fair to 2, and poor to 2 of the studies based upon design considerations. One study received *external validity* rating of good, three were fair while two were rated as poor, Table 3.

Thus, the frequency of mild macrocytosis, mild anemia and mild neutropenia may be common in adults with DS, but prevalence rates are difficult to calculate. The functional consequence of such changes is difficult to predict and likely reflects severity and the specific etiology. Macrocytosis for example, is often clinically benign but could mask the presence of iron deficient anemia which is characterized by microcytosis (Dixon et al. 2010). Similar hematologic findings including neutropenia and macrocytosis have been described in children and adolescents with DS (Dixon et al. 2010).

3.6 | Dysphagia

Two of the five studies on dysphagia used a cohort design (II-2) (Jasien et al. 2016; Smith et al. 2014). Three utilized a case–control design (Hashimoto et al. 2014; Thacker et al. 2008; Zarate et al. 2001) (III). A single study employed prospective screening of their participants (Jasien et al. 2016) but included no controls. Participants were largely ascertained through convenience samples including, medical clinics, community dwelling and residential facilities. The cumulative number of DS participants reviewed was small (*N* = 287) as were the controls (*N* = 378). All articles were published between 2001 and 2016, and addressed KQs 1–2, Table 2.

The data we reviewed was ascertained using a variety of methods including caregiver surveys, direct mealtime observation, water swallow test, esophagram, and tongue pressure measurements. Medical co-morbidities such as poor dental status, tooth loss, known temporomandibular joint dysfunction (TMJ), deglutination disorder, h/o GI surgery were considered reasons for exclusion in some studies. Achalasia, abnormal dentition (missing teeth), were identified as possible risk factors for dysphagia (Smith et al. 2014; Zarate et al. 2001).

Two studies received an *internal validity* rating of fair and three were rated as poor. The *external validity* or generalizability of the findings received a rating of fair in two studies and good in three, Table 3.

Because of differences in methodology and ascertainment it is difficult to compare findings across studies.

4 | DISCUSSION

In this study, we identified six medical conditions that are frequently the focus of clinical concern: hip dysplasia, menopause, acquired cardiac valve disease, type 2 diabetes mellitus, hematologic disorders, and dysphagia. The total number of studies available for review was quite small and the quality of those studies was generally poor to fair. Many studies predated the 1990s before the availability and dissemination of health care guidance for children with DS (AAP 1994). Differences in study sample ascertainment and research design made it difficult to estimate disease prevalence and severity. Further, we were unable to determine the utility of screening asymptomatic individuals for any of the conditions reviewed. It is perhaps of greatest significance that we were unable to identify a single randomized controlled trial from the available literature we searched.

4.1 | Condition specific considerations

4.1.1 | Hip dysplasia

Hip dysplasia is a broadly defined term that encompasses anatomic abnormalities of the ball or socket of the hip joint, congenital or developmental dislocation, and developmental or acetabular dysplasia of the hip. The apparent prevalence of hip dysplasia in adults with DS (5–20%) is higher than in the general adult population (3–4%) (Jacobsen et al. 2005) and higher than in children with DS (Abousamra et al. 2016; Kelley and Wedge 2013). It also has an earlier onset compared to the general population.

Untreated subluxations may become fixed dislocations and the presence of hip disease makes it less likely for an adult with DS to be independently ambulatory. Earlier onset and more rapid progression of disease may lead to the need for total hip arthroplasty (THA) among patients with DS at a younger age. Criteria for THA typically include pain and functional limitations. In the general population, the majority of hip replacements occur in patients older than 65 years, and the need for surgical revision is between 10 and 15% in 10–20 years (Crawford and Murray 1997). In a recent review of adults with DS who underwent THA the surgical revision rate was 7.5% after 5 years, twice that of controls (Sha et al. 2019). The rate of perioperative, medical, and surgical complications in adults with DS is also higher compared to controls (Boylan et al. 2016; Sha et al. 2019).

Currently, screening for hip dysplasia in asymptomatic patients with unchanged gait, may be of little benefit in the absence of interventions to reduce disease progression. Hip dysplasia should be considered in the differential diagnosis of adults with DS presenting with pain or change in activity, such as refusal to walk distances or obvious gait changes (symptomatic). While evaluation with plain radiographs is generally available and sufficient for evaluation, computed tomography (CT) may be needed for both evaluation and surgical planning given differences in the shape of the acetabulum, and differences in the degree of acetabular and femoral ante-version in people with DS. As the life span for people with DS increases and they continue to desire more active lives, intervention using THA is likely to increase (Gross et al. 2013).

Further research regarding the natural history, early detection and prevention of symptomatic hip dislocation in adults with DS appears warranted, and screening protocols for asymptomatic high risk patients should be considered.

4.1.2 | Menopause

Menopause is typically defined as the absence of periods for 12 consecutive months. The average age of menopause for women with DS (late 40s) is approximately 2–3 years earlier than for women in the general population (early 50s) (Schupf et al. 2003). Menopause is associated with a wide range of health effects including, CNS, sleep, metabolic, weight, cardiovascular, musculoskeletal, and urogenital consequences (Monteleone et al. 2018). Some of these symptoms occur in >80% of women (Gracia and Freeman 2018). While some of the studies in this review found an increased risk of dementia associated with an earlier age at menopause transition, the prevalence and severity of related symptoms (hot-flashes, vasomotor changes, cognitive, and mental health), and the risk for associated medical conditions remains underexplored in women with DS (Patel et al. 2001).

None of the studies reported treatment data of menopausal symptoms in women with DS, thus the impact of hormonal replacement therapy (HRT) and non-hormonal treatments on symptoms in this population remains unexplored.

The USPSTF does not presently recommend the use of hormonal replacement therapy (HRT) in post-menopausal women for the prevention of chronic symptoms nor dementia (Gartlehner et al. 2017). However given the >95% risk of early dementia in persons with DS, and the apparent reduced incidence of breast and cervical cancer and hypertension in people with DS, this recommendation should be reconsidered if supportive research evidence is forthcoming (Schupf et al. 2018).

Clinicians may wish to consider menopausal-related symptoms in women with DS >45 years who experience sleep, vasomotor, behavioral, and/or cognitive changes as potentially treatable. Women experiencing severe menopausal symptoms may benefit from the full range of treatment options, for chronic symptoms. These topics require further study prior to making informed recommendations.

4.1.3 | Acquired cardiac valve disease

Approximately 36% of DS subjects had mitral valve disease (prolapse or regurgitation), 10% had tricuspid disease (insufficiency or regurgitation), and 8% had aortic disease (insufficiency or regurgitation). In the single study that employed prospective cardiac screening a subset of participants (N = 138) without known congenital heart defect (CHD), 24 (17%) of these participants were discovered to have previously undiagnosed CHD. Mild to moderate regurgitation was also present in one or more valves (mitral, aortic, pulmonic, and tricuspid) (Vis et al. 2010) and was not associated with age or sex.

The prevalence of adults with DS born with CHD was reviewed by our workgroup previously (Capone et al. 2018). In one of those studies a 75% prevalence of CVD was discovered in those with CHD (Vis et al. 2010). The prevalence rate of CVD in all adults with DS may be up to 50%, which is well above that for the general population (Iung and Vahanian 2014). In children with DS, CVD is associated with CHD such as atrioventricular septal defect, ventricular septal defect and Tetralogy of Fallot (Acar et al. 1999; Tumanyan et al. 2015). Isolated cleft mitral valve can also occur in DS even in the absence of CHD (Hammiri et al. 2016), and its prevalence in DS may be around 6% (Thankavel and Ramaciotti 2016).

Further research to determine the incidence of acquired CVD in adults born with or without CHD could inform the development of screening protocols (Vis et al. 2010).

4.1.4 | Type 2 diabetes mellitus

The prevalence of T2DM in DS as reported in two studies is estimated at 4%–8% (Real de Asua et al. 2014a; Taggart et al. 2013). One study reported an increased risk for developing diabetes in those with DS compared to the general population (Incidence risk ratio = 1.3) but oddly did not specify between type 1 and type 2 diabetes (Alexander et al. 2016). Another study found no patients with DS in their cohort (N = 40) with confirmed T2DM (Ohyama et al. 2000). Regarding comorbidities, the prevalence of diabetic retinopathy is reported in one very small study at one in nine (11%) (Fulcher et al. 1998). Laboratory values available show that those with DS and abdominal obesity were more likely to show signs of insulin resistance (Real de Asua et al. 2014a). A single study found evidence that exercise and diet were useful in preventing diabetes and obesity (Ohyama et al. 2000).

This prevalence rate of T2DM (4–8%) appears to be lower than would be predicted based upon the prevalence of moderate–severe obesity reported in this population (Capone et al. 2018). There is no literature available on the screening or management of T2DM in persons with DS. Future research should focus on development of a standardized screening protocol and assessment tools. Studies in children and adolescents with DS show that insulin resistance is associated with obesity, female gender, and leptin resistance (Yahia et al. 2012; Fonseca et al. 2005). Both leptin levels and leptin resistance has also been shown to be higher in children with DS compared to typical controls (Tenneti et al. 2017). In one study of adults with DS (N = 48) higher levels of fasting insulin, and insulin resistance were reported compared to controls (N = 33) but were non-significant when adjusted for age and gender (Real de Asua et al. 2014a, 2014b). If confirmed by larger studies in adults, this apparent lower prevalence of T2DM could suggest protective factors that modulate the risk for T2DM in this population.

It will be important to expand research to include all known disease risk factors and modifiers such as adiposity distribution, and the role of neuroendocrine and inflammatory mechanisms (Gonzalez et al. 2018). Determining which biomarkers are most useful for understanding physiologic mechanisms and the search for effective biomedical interventions are considered high priority (Bertapelli et al. 2016).

4.1.5 | Hematologic

The frequency of mild macrocytosis, mild anemia, and mild neutropenia may be common in adults with DS, but prevalence rates are difficult to calculate. The functional consequence of such changes is also difficult to predict and likely reflects both clinical severity and specific etiology. Macrocytosis in the absence of vitamin B12 or, is often considered clinically benign but could mask the presence of iron deficient anemia which is characterized by microcytosis (Dixon et al. 2010). Similar hematologic findings including neutropenia and macrocytosis have been described in children and adolescents with DS (Dixon et al. 2010).

Screening parameters and management of hematologic disorders has not been thoroughly considered in adults with DS. Medical comorbidities such as GERD associated esophagitis, celiac disease, liver disease, menorrhagia, and untreated obstructive sleep apnea with nocturnal hypoxemia may affect red blood cell (RBC) indices in the general population. Further research is required to document such changes if present in DS.

A recent metabolomics study of RBCs in subjects with DS (N = 30) and control subjects (N = 67) revealed subtle differences in specific metabolites related to glycolysis, purine catabolism, glutamine/glutamate homeostasis, products of transamination, and other carboxylic acids (Culp-Hill 2017). Widespread dysregulation of RBC metabolism, included intracellular accumulation of lactate, amino acids (except methionine), purine catabolites, glutathione metabolites, carboxylic acids, bile acids (conjugated), and acyl-conjugated carnitines were found. Perhaps such subtle changes reflect a metabolic phenotype.

4.1.6 | Dysphagia

In the studies reviewed, a majority >50% adults with DS may be at increased risk for choking, associated with meals and drinking but a prevalence cannot be calculated.

Co-morbid conditions which place individuals with DS at risk for dysphagia include, oral and dental abnormalities (Faulks et al. 2008; Hennequin et al. 1999) GERD and a variety of esophageal abnormalities (Real de Asua et al. 2015; Wallace 2007; Zarate et al. 1999). Additionally, cervical spine surgery (Siemionow et al. 2017) and achalasia (Zarate et al. 1999) have both been associated with dysphagia and aspiration specifically in adults with DS.

It is unclear what methods should be used when screening for dysphagia or aspiration in this population. In clinical practice, screening questions about mealtime associated symptoms could easily become a part of the routine medical history at annual visits. Direct mealtime observation in conjunction with video-fluoroscopic swallow study (VFSS) probably represents the gold-standard for evaluating dysphagia, however fiber-optic endoscopic evaluation (FEES) is increasingly being used because it can provide information about the effects of dietary modification on swallowing (Wirth et al. 2016).

Because of the high risk for respiratory infections and associated mortality in elderly persons the relationship between dysphagia, aspiration and pneumonia requires extreme clinical vigilance and deserves further study (Bittles et al. 2007; Englund et al. 2013; Lazenby 2008). In elderly adults with DS (>45 years) new-onset seizures, stroke, Parkinsonism, dementia and medications are additional risk-factors which have not been thoroughly investigated (Altman et al. 2013).

Recent lessons learned about dysphagia in children with DS can further our understanding of this condition in adults. High rates of both symptomatic and silent aspiration have been demonstrated in children with DS (Jackson et al. 2016; O'Neill and Richter 2013). Many of these children had cardiac, gastrointestinal, pulmonary, and tracheal malformations requiring surgical repair in early childhood. It is

likely that some of these individuals carry this propensity for dysphagia into adulthood (Kallen et al. 1996; Kohr et al. 2003).

5 | LIMITATIONS

The total number of studies available for review was quite small and the quality of those studies was generally poor to fair. Many studies predated the 1990s before the availability and dissemination of health care guidance for children with DS (AAP 1994). Additional limitations include, the restriction of our review only to that literature written in English and available through the NLM PubMed. The studies available for review were generally poor to fair, especially those relying on data collected retrospectively from chart reviews, or those using convenience samples without controls. Further, the sample size of many studies was quite small and not useful for making statistical comparison across studies. In most rigorous systematic literature reviews, such articles would have been excluded.

The KQ addressed in the literature was very limited indeed, primarily focused on KQ 1, 2 rarely 3 and the quality of this evidence is not very good. We have identified major gaps in our knowledge concerning the preferred, most effective means of screening high-risk individuals, and whether doing so impacts on morbidity or mortality. As such, the financial costs, potential risks and benefits of screening is largely unknown., Many studies were performed in a medical or residential setting because that is where one finds large numbers of adult individuals with DS. Thus, ascertainment bias will result in oversampling the most symptomatic individuals with severe disease. However, individuals with severe disease are probably not uncommon in the primary care setting. Many community-based physicians face the same challenges trying to evaluate and manage complex patients with DS as do specialty centers. It is the community-based primary care providers who will benefit most from having clinical guidance documents to assist in clinical decision making. A single reviewer extracted the data from each article and summarized the findings before it was re-reviewed by a panel of expert practitioners experienced in caring for adults with DS. Inter-rater reliability was not assessed. Despite these limitations, the study represents a coordinated effort by leading medical experts to critically review and synthesize the existing and emerging knowledge to best inform health screening and evaluation practices for adults with DS.

5.1 | The adult population in perspective

The number of persons with DS living in the U.S.A. (2008–2010) is estimated to be between 200,000 and 250,000 (de Graaf et al. 2017; Presson et al. 2013); and the number of adults (>18 years) with DS living in the U.S.A. approaches or exceeds 125,000 individuals.

As longevity continues to increase it is also expected that greater numbers of adults with DS will live to be of advanced-age (>45 years) (Bittles and Glasson 2004). This presents ongoing challenges to the primary care physicians expected to manage an array of congenital, chronic and age-related conditions. Previously, we identified seven conditions that were highly prevalent (>50%) in this population (Capone et al. 2018). In this study, we identified six more conditions that although less prevalent than the original seven, remain the focus of clinical concern: hip dysplasia, menopause, acquired cardiac valve disease, type 2 diabetes mellitus, hematologic disorders, and dysphagia. Differences in how the study samples were ascertained usually from disparate sources (home-community, residential facility, or clinical samples) and the research design (case series, case–control, or cohort design) made it difficult to estimate disease prevalence for any condition.

5.2 | Strategic planning

For planning purposes and informed by this review, we estimate that the number of adults (>18 years) with DS currently living in the U.S.A. with a specific co-occurring health condition can be determined by the following: estimated disease prevalence in the DS population (rounded up to the nearest 5%) × 125,000 estimated individuals (>18 years) living in the U.S.A. = number of individuals with DS affected by the condition. However, these figures represent crude estimates only and are probably unsuitable for public health planning. Thus for hip dysplasia (20%) = 25,000; menopause (50%) = 62,500; cardiac valve disease-independent of CHD- (50%) = 62,500; type 2 diabetes (8%) = 10,000; and dysphagia (50%) = 62,500.

In clinical practice, multiple medical co-morbidities is the rule not the exception, and this entails complex decision-making and management considerations (Evenhuis et al. 2013; Schoufour et al. 2014). Taken together, these factors suggest a modified approach to both diagnosis and treatment in elderly or medically frail adults with DS. In such situations, assessment of the specific risks and potential benefits of diagnostic evaluation and its intended therapeutic purpose needs to be discussed openly with decision-makers. Management strategies for those of advanced-age or nearing end-of-life need to be made available to healthcare providers and family decision makers to use as they see fit in their specific circumstances.

5.3 | Toward guidelines

The biggest challenge for guideline development is their intended scope, breadth and depth. As DS is not a specific disease, but rather a unique human condition associated with a variety of developmental-anatomical differences, acquired (chronic) medical conditions, and precocious aging, such guidelines would potentially involve every major organ system and life-stage. Due to the biologic underpinnings of trisomy 21 some medical conditions may exhibit unique features of etiology-pathogenesis and natural history compared to individuals without this chromosomal condition (Zigman 2013). The best precedent for creating guidance documents has come from the efforts of the American Academy of Pediatrics (AAP 2011). Although guidance beyond 21 years is not within the scope of the AAP document, it

never-the-less serves as an important educational tool about DS that would be of benefit to any health care provider (physicians, nurses, nurse practitioners and physician assistants) who will be providing direct care to adults (Qaseem et al. 2010).

Stakeholder groups including caretakers (parents, siblings, and agency workers) and advocacy organizations (national and regional parent groups) who will use this information to advocate for quality health care locally and nationally (IOM 2011) should also be included in the review process particularly in determining whether an assessment of benefits, harms, and potential alternative options are fully addressed (Diaz Del Campo et al. 2011). Deployment of invested stakeholders will be critical to the prompt dissemination and successful adoption of health guidelines in both the public health and primary care settings (Luke et al. 2013).

5.4 | Realigning clinical research

It is likely that the prevalence rate for most co-occurring conditions is well within the range of rare disease designation (frequency < 200,000) (National Institutes of Health 2017). And so, it remains challenging to plan, organize, and enroll sufficient numbers of adult participants into existing data collection efforts and screening protocols, in part because of their numbers and geographical distribution.

It is not known what percent of the estimated 125,000 adults with DS living in the U.S.A. utilize services at an existing specialty clinic. Those who do almost certainly receive more comprehensive care compared to those who do not (Jensen et al. 2013; Skotko et al. 2013). Although the number of DS clinics serving the needs of adults are few, many are located at large, university-affiliated medical, research and training centers (AUCD 2017; DSMIG-USA 2019). Despite these apparent advantages, clinical research on adults has not kept pace with the need for relevant information. What is required are better efforts to organize and support existing clinical programs to collect and share information on medical screening, diagnostic evaluation and treatment outcomes, as routinely performed at the point of care. Recent efforts to conduct multicenter data collection and sharing using clinician input data are successfully underway (Lavigne et al. 2015, 2017) and may provide the necessary mechanism for further progress if properly funded. Efforts to engage the larger community of families living with DS to participate in clinical research studies is also underway (Peprah et al. 2015). The availability of research funding commensurate with stated long-term goals has only recently been realized (NICHD 2014).

In 2018, the National Institutes of Health (NIH) announced a new trans-NIH initiative to advance the understanding of medical conditions associated with DS. The INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome (Project INCLUDE) was announced with three major goals, (a) targeted high-risk, high-reward basic science studies; (b) development of a DS cohort to perform deep-phenotyping and to study co-existing conditions; and (c) to establishing a clinical trials network (National Institutes of Health 2018).

Project INCLUDE will investigate conditions that affect individuals with DS as well as the general population, such as Alzheimer's disease/dementia, autism, cataracts, celiac disease, congenital heart disease, diabetes, and immune dysfunction. The creation of evidence-based guidelines based upon new research and reviews such as ours is the logical next step to "Improving health and well-being of individuals with DS" in line with the NIH INCLUDE initiative.

Presently, the availability of dedicated research personnel and lack of infrastructure support each represent limiting factors in advancing a truly comprehensive data collection effort and person-centered research strategy. While the provision of high quality clinical care to persons with DS is challenging enough, it is yet another matter to capture this experience for the purpose of informing evidence-based care (Murillo et al. 2006). With the necessary support and leadership, it is well within the capacity of existing clinical programs to address this urgent need (Carfi et al. 2015; McCabe et al. 2011; Real de Asua et al. 2015).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Each of the authors contributed equally in performing a literature review, data extraction and initial data summation. George Capone, Brian Chicoine, and Peter Bulova established the methodology and procedure for literature review and data acquisition. They also led the work group initiative from its conception and provided mentoring to junior authors. George Capone, Mary Stephens, and Stephanie Santoro wrote and edited the manuscript and tables. All authors participated in reviewing the text prior to submission.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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