

## ORIGINAL ARTICLE

# Cognition in adults with Williams syndrome—A 20-year follow-up study

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## Abstract

**Background:** Williams syndrome (WBS) is a genetic multisystem disorder. The main symptom is borderline (intelligence quotient, IQ 70–79) or abnormally low intelligence (IQ < 70). According to earlier studies young individuals with WBS demonstrate generally a slightly higher verbal IQ (VIQ) compared to performance/nonverbal IQ (PIQ). WBS was recognized as a distinct entity already about 60 years ago, but still cognition in adults with WBS is poorly known.

**Methods:** We followed 25 adults (age at baseline 19–68, median 38) with genetically confirmed WBS for about 20 years. The study subjects underwent medical and neuropsychological assessments at the baseline and at the end of follow-up.

**Results:** The mean VIQ remained quite stable from early adulthood up to 40 years of age after which it declined. The mean PIQ kept on improving from early adulthood until 50 years of age after which it gradually declined. At the end of the study, all study subjects had at least two longstanding health problems out of which hypertension, psychiatric disorder, and scoliosis or kyphosis occurred most frequently. At end of the study, two patients suffered from vascular dementia. Seven patients died during the follow-up.

**Conclusions:** In adults with WBS, the course of cognition is uneven across the cognitive profile. Their verbal functions both develop and deteriorate earlier than performance/nonverbal functions. Frequent somatic co-morbidities may increase risk to shortened life span.

## KEYWORDS

aging, cognition, intellectual disability, Williams syndrome

## 1 | INTRODUCTION

Williams syndrome (WBS, OMIM number #194050), with an estimated prevalence ranging from 1:7,500 to 1:20,000, is a genetic multi-system disorder. It is caused

by hemizygoty at chromosomal site 7q11.23 (Brewer & Morrison & Tolmie, 1996; Poher, 2010). Various somatic comorbidities and symptoms include characteristic facial features and body structure, cardiovascular disease (supravalvular aortic stenosis, hypertension), connective tissue

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abnormalities and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty) (Morris, Demsey, Leonard, Dilts, & Blackburn, 1988; Pober, 2010). The main neuropsychiatric symptom is intellectual disability (ID), which can range from severe to mild. The behavioral phenotype includes pronounced weaknesses in visuospatial construction and relative strengths in auditory short-term memory face processing and expressive language, especially vocabulary (Martens, Wilson, & Reutens, 2008). Many age related medical conditions in WBS appear much earlier than expected, in late adolescence or young adulthood. These include premature graying of the hair, diverticulosis, diabetes mellitus, hypertension, and sensorineural hearing loss. With advancing age, adults are also prone to joint contractures and hyperreflexia, and they often become even more unsteady with such motoric tasks as stepping up or down stairs (Pober, 2010). Standardized testing in young adults demonstrates that their mean verbal intelligence quotient (VIQ) is slightly higher than their mean performance intelligence quotient (PIQ) and full-scale intelligence quotient (FSIQ) (Boaddaert et al., ; Howlin, Davies, & Udwin, 1998; Martens et al., 2008; Mervis, Kistler, John, & Morris, 2012; Searcy et al., 2004) and some earlier studies suggest that FSIQ remains stable over an individual's lifetime (Ficher, Lense, & Dykens, 2016; Howlin et al., 1998; Howlin, Elison, & Udwin, 2010; Martens et al., 2008; Searcy et al., 2004). Although WBS was already recognized as a distinct entity about 60 years ago, the cognition in adults carrying this genetic defect continues to be poorly known (Ficher et al., 2016; Howlin et al., 2010; Searcy et al., 2004). Our study attempted to fill this gap in knowledge by elucidating prospectively the cognitive functions and the state of health in adults with WBS during a 20-year clinical follow-up.

## 2 | SUBJECTS AND METHODS

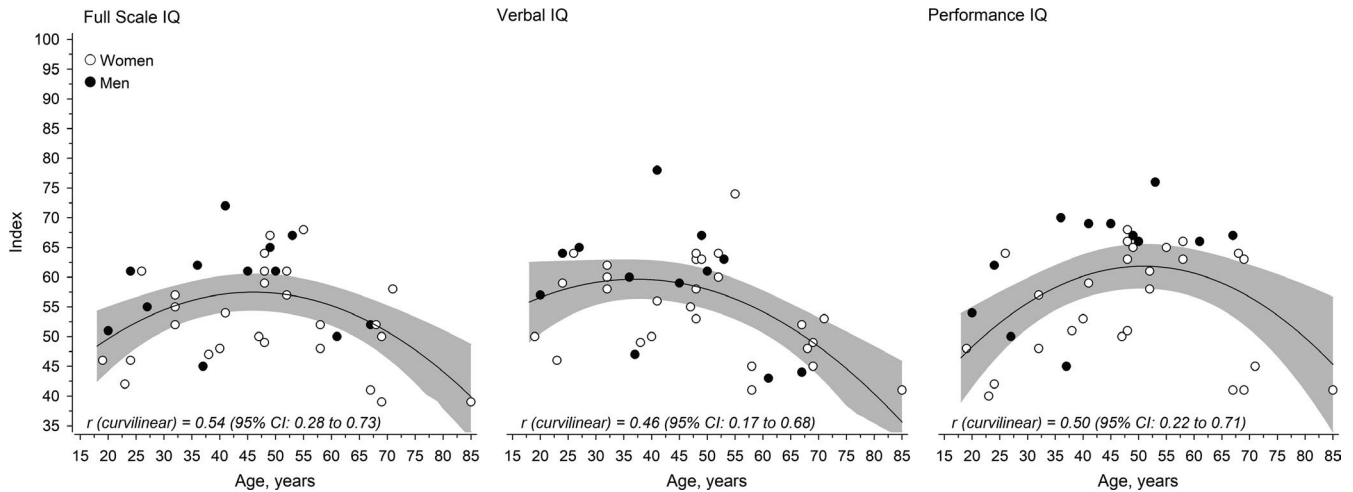
Finland is divided into 16 state-supported regional service districts for individuals with an ID. Initially, all 34 identified adults from South Häme, Pirkanmaa, and Northern Ostrobothnia districts with clinically and genetically confirmed WBS were invited to participate in the study. The authors, that is, neuropsychologist, clinical psychologist, and neurologists assessed the study subjects at baseline and at end of the follow-up.

The psychologist (OS and VK) chose the most suitable testing method for each patient based on a case-by-case consideration and used the same individually chosen test throughout the follow-up. The cognitive test battery included three Wechsler tests: (WAIS-R, [Wechsler, 1992], WISC-R, [Wechsler, 1984], and WPPSI-R, [Wechsler, 1995]); Leiter International Performance Test (LIPS, [Leiter, 1980]) and Bayley Scales of Infant Development,

**TABLE 1** The state of health of the 25 study subjects with WBS at the baseline and at end of the follow-up

	Baseline N (%)	End N (%)
<i>Cardiovascular co-morbidity</i>		
Heart defect	4 (16)	10 (40)
Hypertension	5 (17)	17 (68)
Hypercholesterolemia <sup>a</sup>	?	9 (36)
<i>Neurological co-morbidity</i>		
Epilepsy	1 (3)	3 (12)
Vascular dementia	0	2 (8)
Transient ischemic attacks	0	5 (20)
Migraine	0	3 (12)
Sleep apnea <sup>b</sup>	0	2 (8)
Dystonic movement disorder	2 (8)	6 (24)
<i>Gastrointestinal co-morbidity</i>		
Diverticulitis	1 (3)	8 (32)
Coelicia <sup>c</sup>	0	2 (8)
Gastrointestinal reflux	0	6 (24)
Constipation	4 (16)	5 (20)
Rectal prolapse	2 (8)	7 (28)
<i>Psychiatric disorder</i>		
Bipolar mood disorder	2 (8)	2 (8)
Anxiety disorder	3 (12)	3 (12)
Unspecified psychiatric disorder	7 (28)	11 (44)
<i>Autoimmune co-morbidity</i>		
Hypothyroidism	1 (3)	6 (24)
Diabetes type 2	2 (7)	7 (28)
Rheumatoid arthritis	1 (3)	2 (8)
<i>Sensory impairment</i>		
Auditory defect	2 (8)	7 (28)
Visual impairment	3 (12)	8 (32)
<i>Skeletal impairment</i>		
Teeth, missing	2 (8)	8 (32)
Scoliosis/kyphosis	8 (32)	11 (44)
Joint luxations	2 (8)	2 (8)
Craniosynostosis-cleft palate	1 (3)	1 (4)
<i>Other</i>		
Cancer	1 (3)	2 (8)
Asthma	0	1 (4)
Chronic urinary infections	1 (3)	2 (8)
Nephrotic insufficiency	1 (3)	1 (4)
Lymphoedema in legs	1 (3)	3 (12)
Hernia	3 (12)	6 (24)
Obesity	10 (40)	7 (28)

<sup>a</sup>blood cholesterol levels were not routinely measured in 1990s. <sup>b</sup>sleep recordings were not done in 1990s. <sup>c</sup>coelicia was not screened in 1990s as often as in 2010s.



**FIGURE 1** Trajectories of full scale IQ, verbal IQ, and performance IQ on WAIS-R/WISC-R in 23 individuals with Williams syndrome

(BSID-II, [Bayley, 2008]). Wechsler tests are comprised of 10–12 subtests measuring VIQ, PIQ, and FSIQ (which is not an average value of VIQ and PIQ but a distinct measurement of overall cognitive performance). WPPSI-R and WISC-R are designed for preschool and school-aged children but are used also for adults with IDs for whom WAIS-R is too demanding. LIPS comprises tasks in which instructions are given through pantomime and require only nonverbal, motor responses. BSID-II consists of both verbal and nonverbal subtests designed for toddlers. LIPS and BSID-II can be applied to severely and profoundly intellectually disabled individuals in all age groups; however, with adults these tests only determine developmental age, not IQ.

The neurologists (MA, AS, and NB-L) examined clinically the patients at the baseline and at the end of the study.

The relationship between IQ and chronological age was estimated by using random-effects (generalized least squares) regression with quadratic term, subject identifier as a random effect. The method accounts for the correlated structure of dependent variables arising from repeated measures over time, controlling for each individual. Bootstrap estimation was used to derive a 95% confidence interval of curvilinear correlation.

The study was approved and reviewed by Pirkanmaa University Hospital District's ethics committee and written informed consent was received from each participant or their caregiver.

### 3 | RESULTS

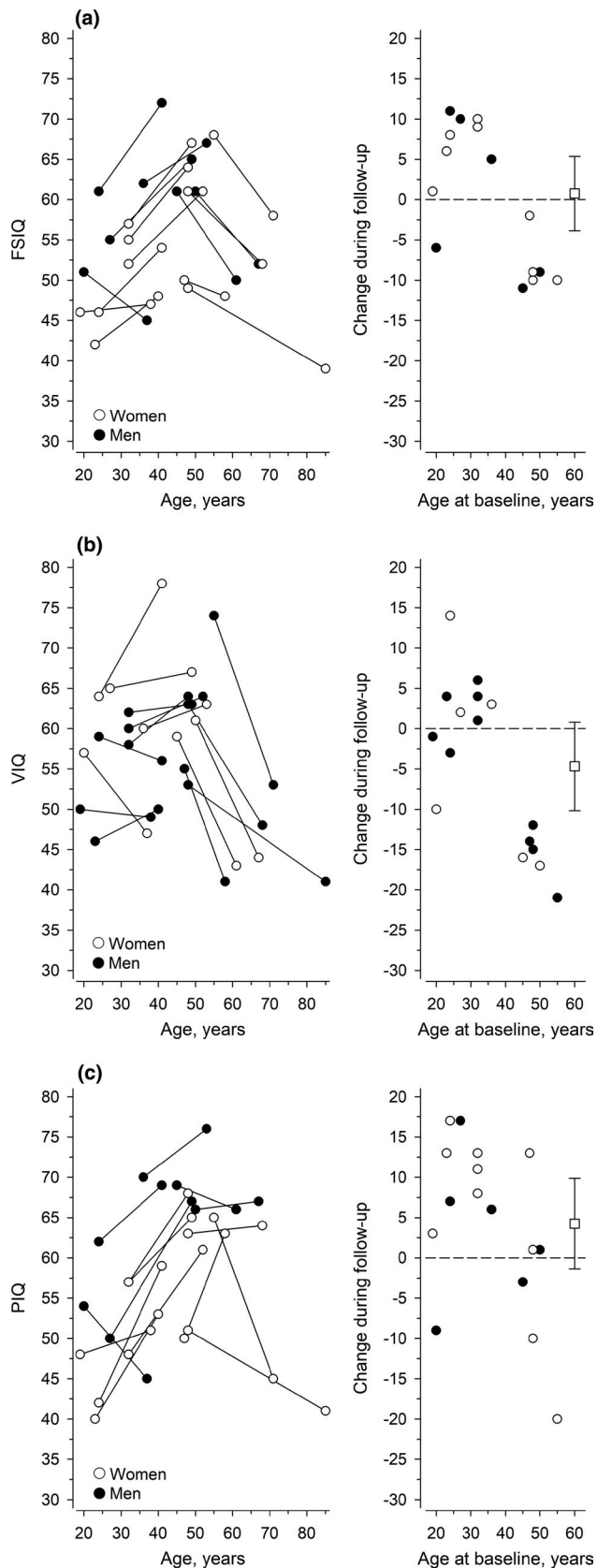
Of the 34 invited persons with WBS, 25 (18 women and 7 men) agreed to participate. At baseline the study subjects' ages ranged from 19 to 68 (median 38) and at end from 39

to 86 (median 52). During the follow-up seven women died and thus were assessed once only. Cardiovascular defects associated with diabetes mellitus type 2 was the cause of death in four women; their ages at death were 64, 68, 75, and 79. Two women had a fatal malignancy; a 27-year-old woman deceased to Hodgkin's disease and a woman aged 60 to myelodysplastic syndrome evolving to leukemia. A 32-year-old woman died of renal insufficiency.

Table 1 presents the state of health of the study subjects at the baseline and at the end of study. By the end of the study all study members had two to eight (median five) longstanding health problems or impairments out of which hypertension, psychiatric disorder, and scoliosis or kyphosis occurred most commonly. Two women suffered from vascular dementia confirmed by brain imaging.

Of the 25, 23 subjects were assessed using WAIS-R or WISC-R, one with LIPS, and one with WPPSI and BSID-II. Figure 1 presents the course of FSIQ, VIQ, and PIQ in 23 study subjects according to their chronological age. In our study group, mean FSIQ and mean PIQ improved between ages 19 to 50, after which age they gradually declined. Mean VIQ remained quite stable from age 19 to 40, after which age it gradually declined. At baseline, median FSIQ was 55, median VIQ 60, and median PIQ 56, while the respective figures at end of follow-up were 53, 52, and 64. Figure 2 presents FSIQs, VIQs, and PIQs of these 23 study subjects at the baseline and at the end of the follow-up and the mean change of IQ scores. There was no difference between genders.

Two patients could not follow verbal instructions and thus were tested with other methods. The developmental age of the 32-year-old man, improved from 4.5 years to 5 years and the developmental age of the 34-year-old woman, declined from 2.8 years to 1.8 years. They both had three health issues; the man had hypertension, hypercholesterolemia, and



**FIGURE 2** Full scale IQ (a), verbal IQ (b), and performance IQ (c) of 23 individuals with Williams syndrome according to chronological age at the baseline, end of the study, and individual changes on WAIS-R/WISC-R scores. Box-and-whisker plot shows 95% confidence intervals of mean change

diverticulitis and the woman had rectal prolapse, gastrointestinal reflux, and hypertension.

## 4 | DISCUSSION

Williams syndrome, like other ID syndromes, is a life-long disorder. During the last decades the life expectancy of people with IDs has increased and thus the number of senior citizens with IDs has grown (Arvio, Salokivi, & Bjelogrić-Laakso, 2017; Arvio, Salokivi, Tiitinen, & Haataja, 2016). Therefore there is a need for research among elderly individuals with IDs (Coppus, 2013).

The strength of our study is a follow-up lasting for 2 decades; much longer follow-ups are not feasible by the same authors. Another strength is the age range of our study group. To our knowledge, to date, the age of the oldest reported study subject with WBS is 52 years (Searcy et al., 2004), while 52 was the median age of the participants at the end of our study. The weakness of our research is the small size of the study group. On the other hand, WBS is a rare condition. Several earlier studies have shown that patients with WBS suffer from several somatic co-morbidities (Coppus, 2013; Pober, 2010). This was also the case among our study subjects and as expected seven out of 25 subjects died during the follow-up. Cardiovascular disease associated with diabetes type 2 was the most common cause of death and malignant disorder the second most common; this is in line with earlier reports (Pober, 2010; Zhukova & Naqvi, 2013). In Finland, the most common causes of death at population are cardiovascular diseases and cancer in people aged over 60 years (Official Statistics of Finland, 2016).

Our study is the first longitudinal clinical follow-up study describing the course of cognition in adulthood. In all but two subjects it was possible to apply the Weschler tests, which have been used in several nonFinnish studies (Boaddaert et al., ; Howlin et al., 1998, 2010; Martens et al., 2008; Searcy et al., 2004). The IQ results of this study representing early adulthood were in line with previous studies confirming that the mean VIQ of 20 to 30 year olds is slightly higher than PIQ. The novel finding of this study is that VIQ begins to deteriorate already after the age of 40, while PIQ and FSIQ continue to improve until the age of 50, after which age they also start to decline.

The relationship between the course of cognition and health can only be speculated because of the small study size and the limited health history that was available. For instance blood cholesterol levels were not routinely checked and coeliac disease, auditory defect, and sleep apnea were not diagnosed as precisely in 1990s as nowadays (Table 1). In addition, it is impossible to know how for example, psychiatric co-morbidities, joint luxations, or hypothyroidism may have influenced the cognition.



In general population the cognitive functions start to decline between ages 60–80 (Salthouse, 2009, 2010a, 2012, 2016; Schaei & Willis, 2010). According to the longitudinal studies so called “crystallized” intellectual functions (i.e., well-learned skills, word, and general knowledge and deductive reasoning) remain quite stable even to age of 70 whereas the “fluid” intellectual functions (i.e., problem solving in novel situations, cognitive processing speed, executive functions, and inductive reasoning) gradually weaken after age of 60 years (Rönnlund & Nilsson, 2006; Salthouse, 2010b, 2012, 2016; Scheie & Willis, 2010). Premature ageing was obvious in our study group consisting of persons with WBS, among whom the mental decline especially in “crystallized” intellectual functions (as determined by VIQ) occurred already after the age of 50. Our next step is to provide more detailed analyses of neuropsychological functioning in persons with WBS to guide and inform organization of services.

## 5 | CONCLUSION

The course of cognition in adults with WBS is different compared to general population. In WBS maximal VIQ is reached by young adulthood age, but PIQ and FSIQ improve until middle age. However, cognitive decline is uneven across the cognitive profile; VIQ declines earlier than PIQ and FSIQ. Life expectancy in WBS may be shortened due to frequent somatic co-morbidities and premature mental aging.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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