

Adulthood in 22q11.2 deletion syndrome

Erik Boot, MD, PhD
ID physician
December 2, 2021



Take home message

➤ All adults with 22q11.2DS need follow-up for

- › Recognition
- › Evaluation
- › Surveillance
- › Management
- › Counseling

of possible chronic diseases



Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome

Anne S. Bassett, MD,* Donna M. McDonald-McGinn, MS, CGC,* Koen Devriendt, MD, Maria Cristina Digilio, MD, Paula Goldenberg, MD, MSW, Alex Habel, MD, Bruno Marino, MD, Solveig Oskarsdottir, MD, PhD, Nicole Philip, MD, Kathleen Sullivan, MD, PhD, Ann Swillen, PhD, Jacob Vorstman, MD, PhD, and The International 22q11.2 Deletion Syndrome Consortium**

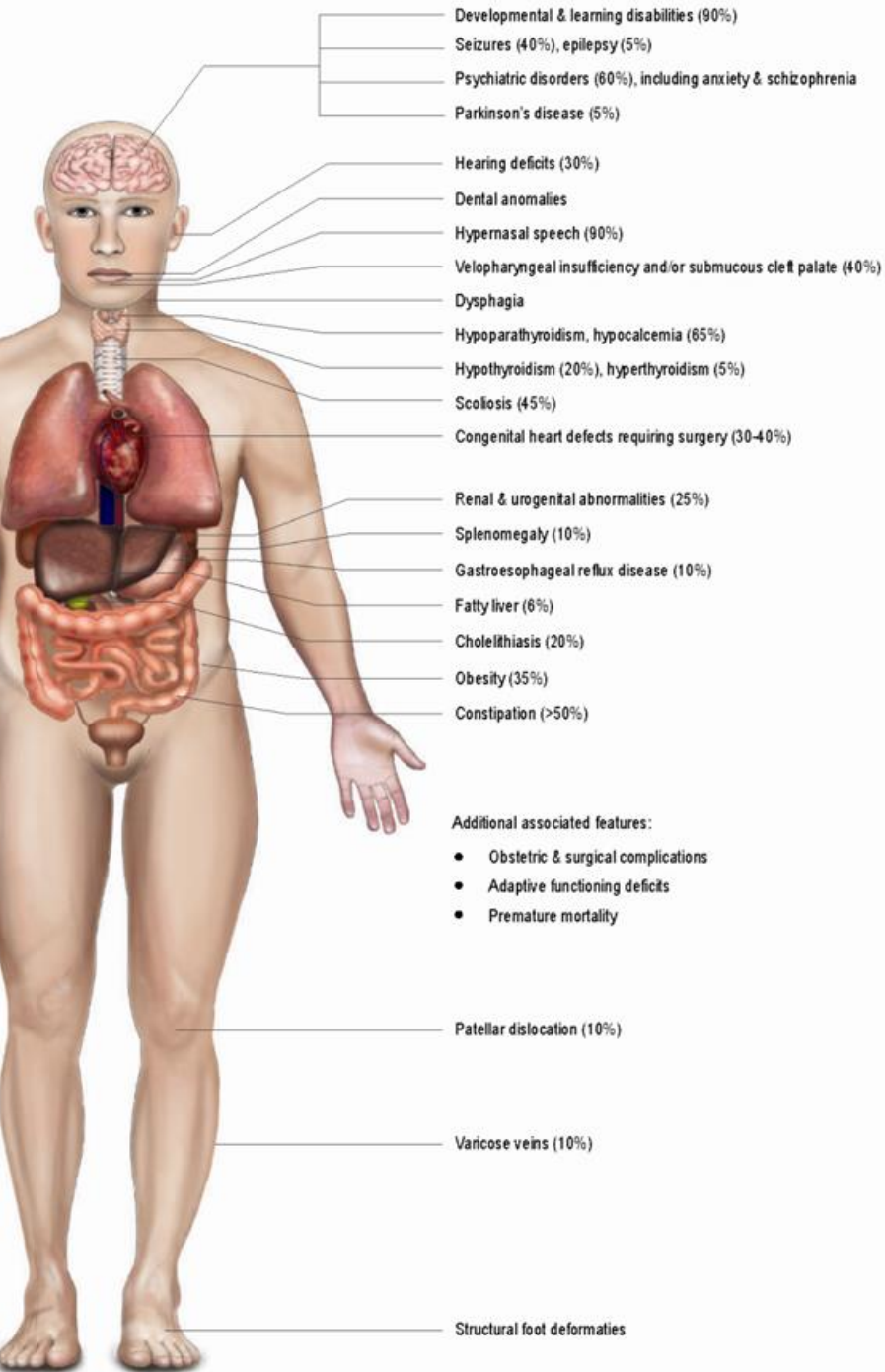
© American College of Medical Genetics and Genomics

REVIEW

Genetics
in Medicine

Practical guidelines for managing adults with 22q11.2 deletion syndrome

Wai Lun Alan Fung, MD, ScD¹⁻⁴, Nancy J. Butcher, MSc^{2,5}, Gregory Costain, PhD^{2,5}, Danielle M. Andrade, MD, MSc^{1,6}, Erik Boot, MD, PhD^{1-4,7}, Eva W.C. Chow, MD, FRCPC^{2,4}, Brian Chung, MDCPCH, MBBS⁸, Cheryl Cytrynbaum, MS, CGC⁹, Hanna Faghfoury, MD¹⁰, Leona Fishman, MD, FRCPC⁹, Sixto García-Miñaur, MD¹¹, Susan George, MD, FRCPC^{1,12,13}, Anthony A. Lang, MD, FRCPC^{6,14}, Gabriela Repetto, MD¹⁵, Andrea Shugar, MS, CGC⁹, Candice Silversides, MD, FRCPC^{1,16,17}, Ann Swillen, PhD^{18,19}, Therese van Amelsvoort, MD, PhD²⁰, Donna M. McDonald-McGinn, MS, CGC²¹⁻²³ and Anne S. Bassett, MD, FRCPC^{1-5,12,17}



Multisystem condition

- Considerable variation in **spectrum** of its expression
- Considerable variation in **severity** of its expression
- Cardinal features **change** with increasing age
 - › Congenital
 - › Early-onset
 - › Late-onset

Transition to adult care

- › Vulnerable time
 - › At risk for adverse social and medical outcomes
 - › Emotional immaturity
- › Transition planning
 - › Stepwise approach
 - › Multidimensional needs (continued education and vocational training, employment, healthcare)



Psychosocial challenges subjects with a 22q11.2 deletion my face



Finances



Housing



Social skills



Mental Health



Academics/
Employment

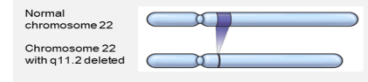
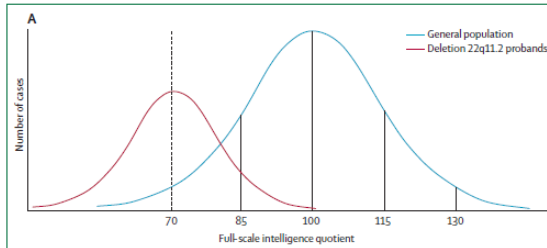


Sexual and reproductive health

- Limited knowledge about sexual health and genetic risk to offspring
- Risk of unplanned pregnancies and sexually transmitted infections (STIs)
- Increased risks and potential complications during pregnancy, delivery, and postpartum periods
- Routine assessments
 - › Counselling and education
 - › STI and cervical cancer screening

Neuropsychiatric expression of 22q11.2DS

Learning- and intellectual disabilities (~90%)



Cognitive deterioration

Early-onset Parkinson's disease

Parkinsonism

Other movement disorders

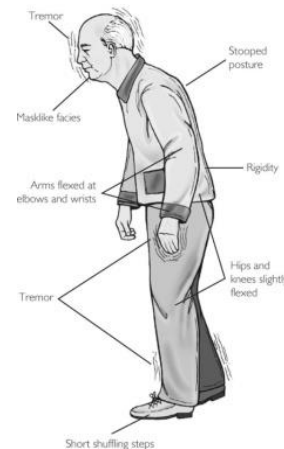
Recurrent seizures (~16%)

Epilepsy (~4%)

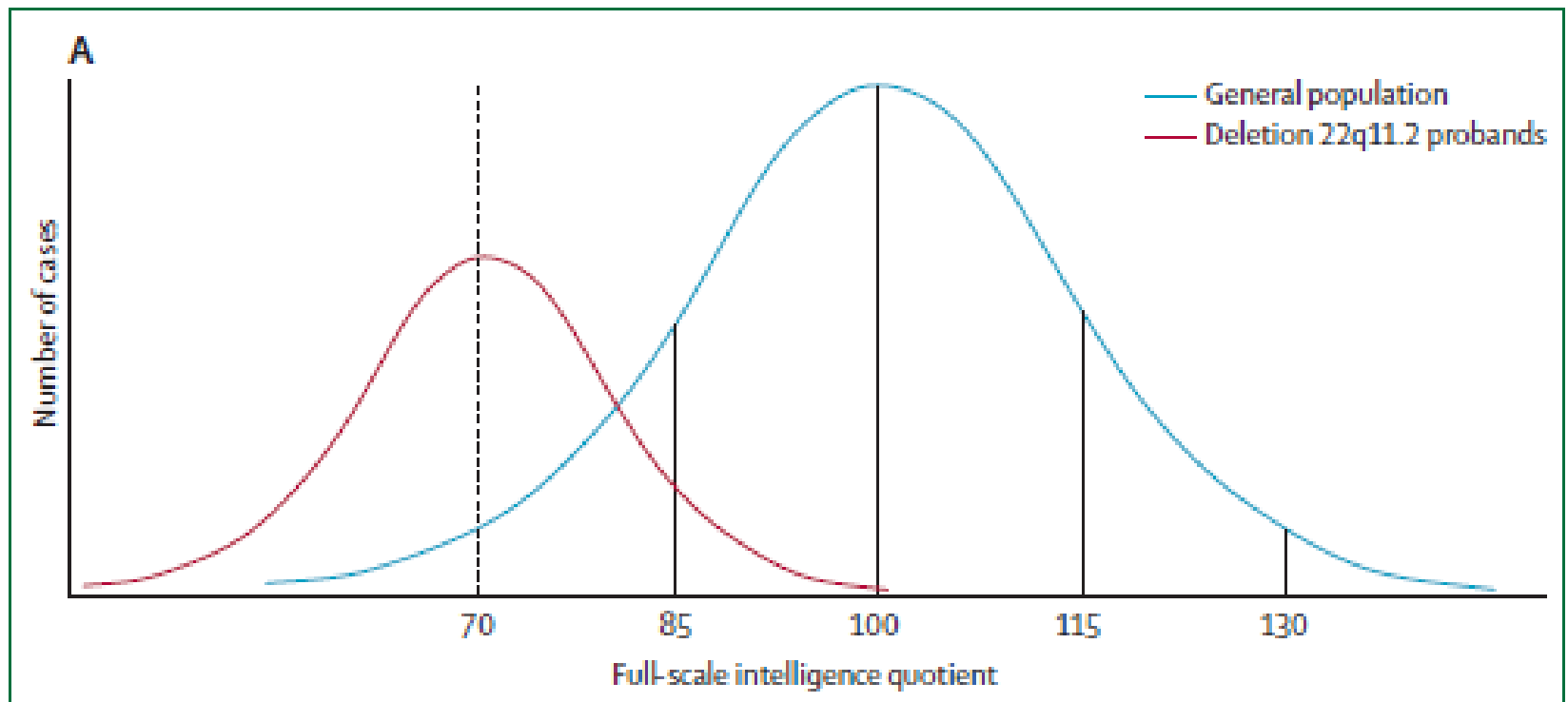


Psychiatric disorders:

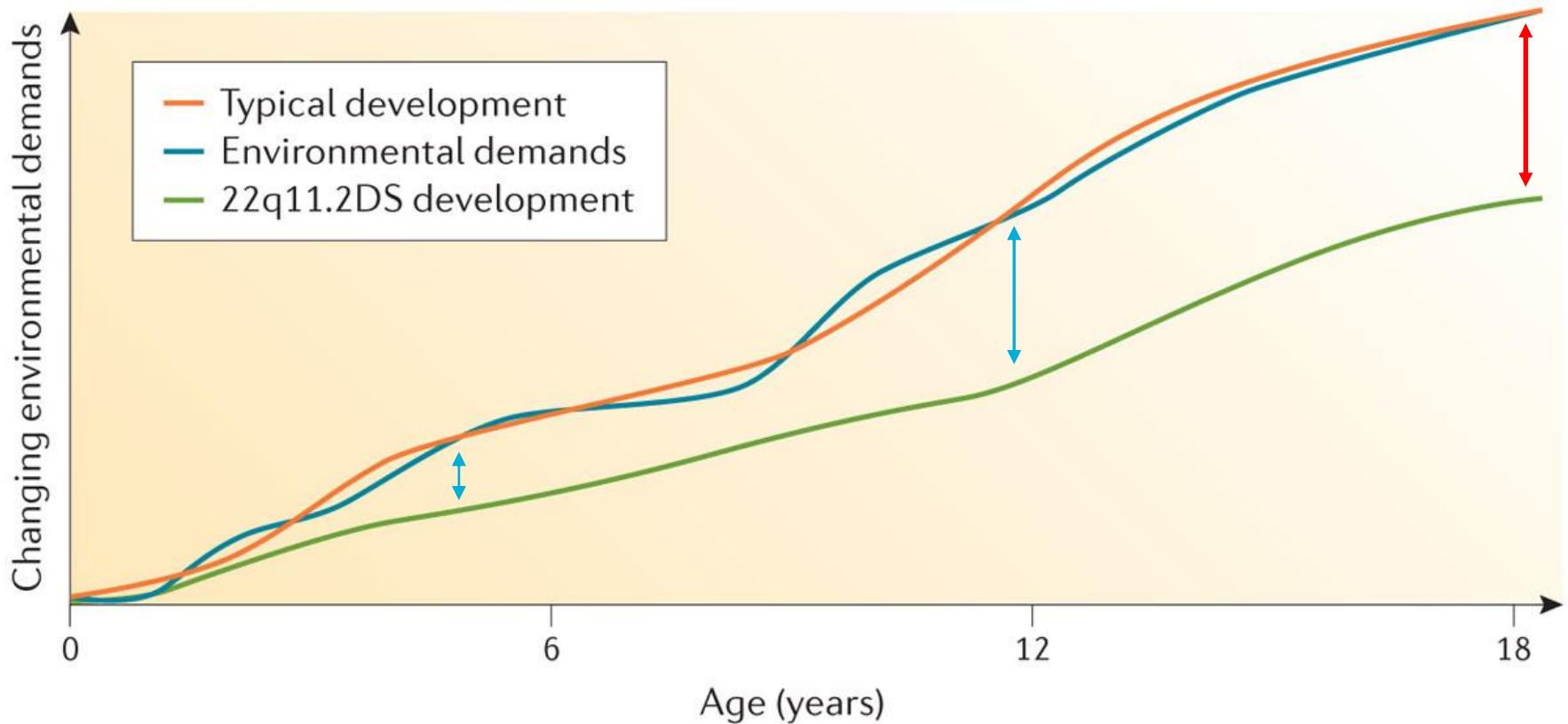
- Autism spectrum disorders
- Attention deficit disorders
- Mood and anxiety disorders
- Psychotic disorders / schizophrenia



Intellectual functioning



Developmental trajectory in 22q11DS: *growing into deficit*



McDonald-McGinn, D. M. *et al.* (2015) 22q11.2 deletion syndrome
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.71

Nature Reviews | **Disease Primers**

Psychiatric disorders

- Anxiety disorders
- Psychotic disorders
- ADHD and autism spectrum disorders may persist in adulthood
- Catatonia
- Substance use disorders less common

22q11.2DS and schizophrenia

- 1-2% of patients with schizophrenia has a 22q11.2 deletion
- In 22q11.2DS:
 - › 20-fold increased risk to develop schizophrenia
 - › 30% psychotic disorder
 - › 25% schizophrenia



Neurological disorders

- › Seizures / epilepsy
- › Parkinsonism
 - › Parkinson's disease
- › Other movement disorders and abnormalities
- › Neurodegenerative processes / decline in overall functioning



Seizures / epilepsy

- Epilepsy: 4-fold increased risk compared to general population
 - › Structural (malformations of cortical development, acquired trauma, strokes)
- Seizures:
 - › Lowered seizure threshold
 - › Symptomatic (e.g., hypocalcemia, fever, antipsychotics)
 - › Generalized tonic-clonic, absences, myoclonic, focal with preserved or impaired awareness

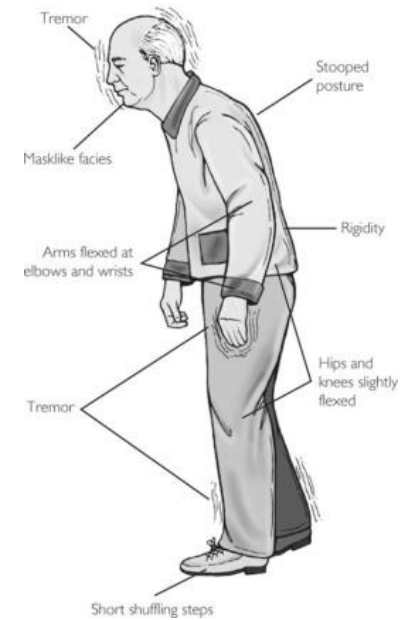
Parkinsonism

Core parkinsonian features:

- Bradykinesia
- Rigidity
- Rest tremor

Causes:

- Parkinson disease (**progressive**, neuronal cell death)
- Medication-induced (**reversible**, esp., antipsychotics)
- Other



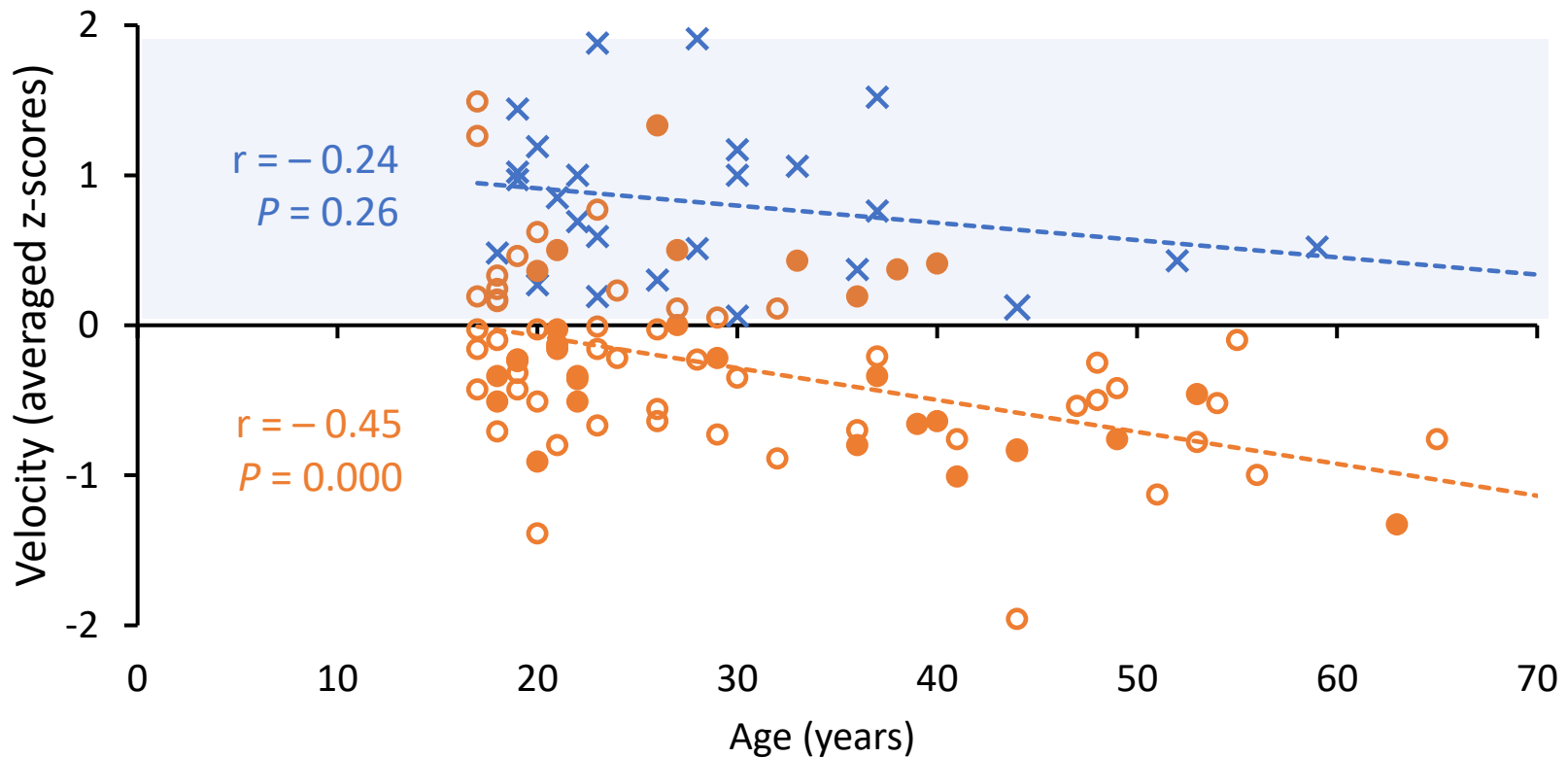
Source: Brainmind.com



Parkinson's disease

	General population	22q11.2DS
Prevalence	1-2% (>60 yr)	6% (36-64 yr)
Male-female-ratio	~2:1	~2:1
Response to L-DOPA	Good	Good
Hallmark symptoms (bradykinesia, rigidity, rest tremor)	Yes	Yes
Neuropathological features	Yes	Yes
Average age at motor onset	~60 yr	~40 yr
	<i>Antipsychotics may delay diagnosis</i>	

Bradykinesia in adults with 22q11.2DS



Movement disorders and abnormalities

Dystonia	11%
Myoclonus	8%
'Generalized shakiness'	7%
Tic disorders	5%
Functional neurological disorders	3%

There is a spectrum of movement disorders and abnormalities in adults with a 22q11.2 microdeletion

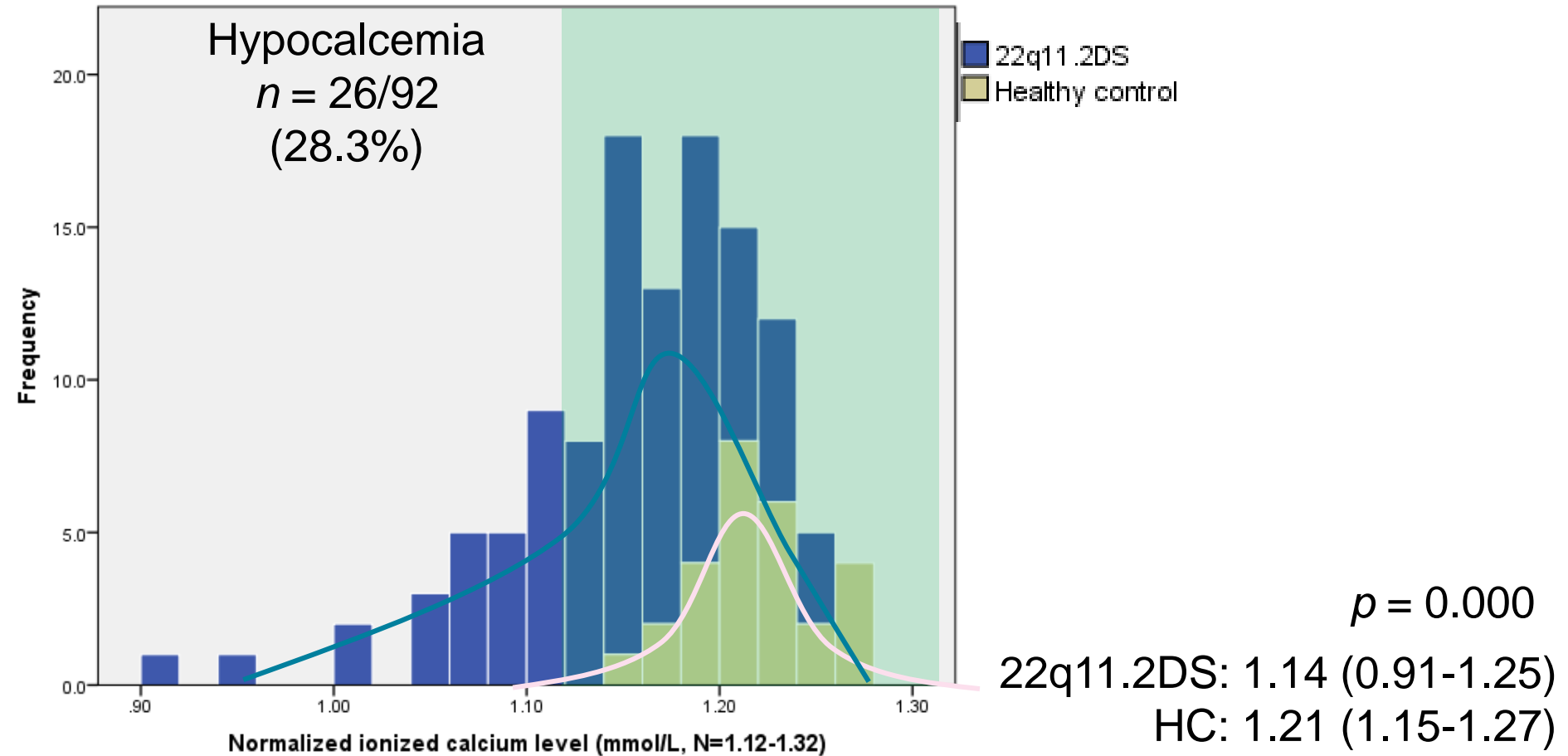
Endocrinology and metabolism

Estimates of lifetime prevalences:

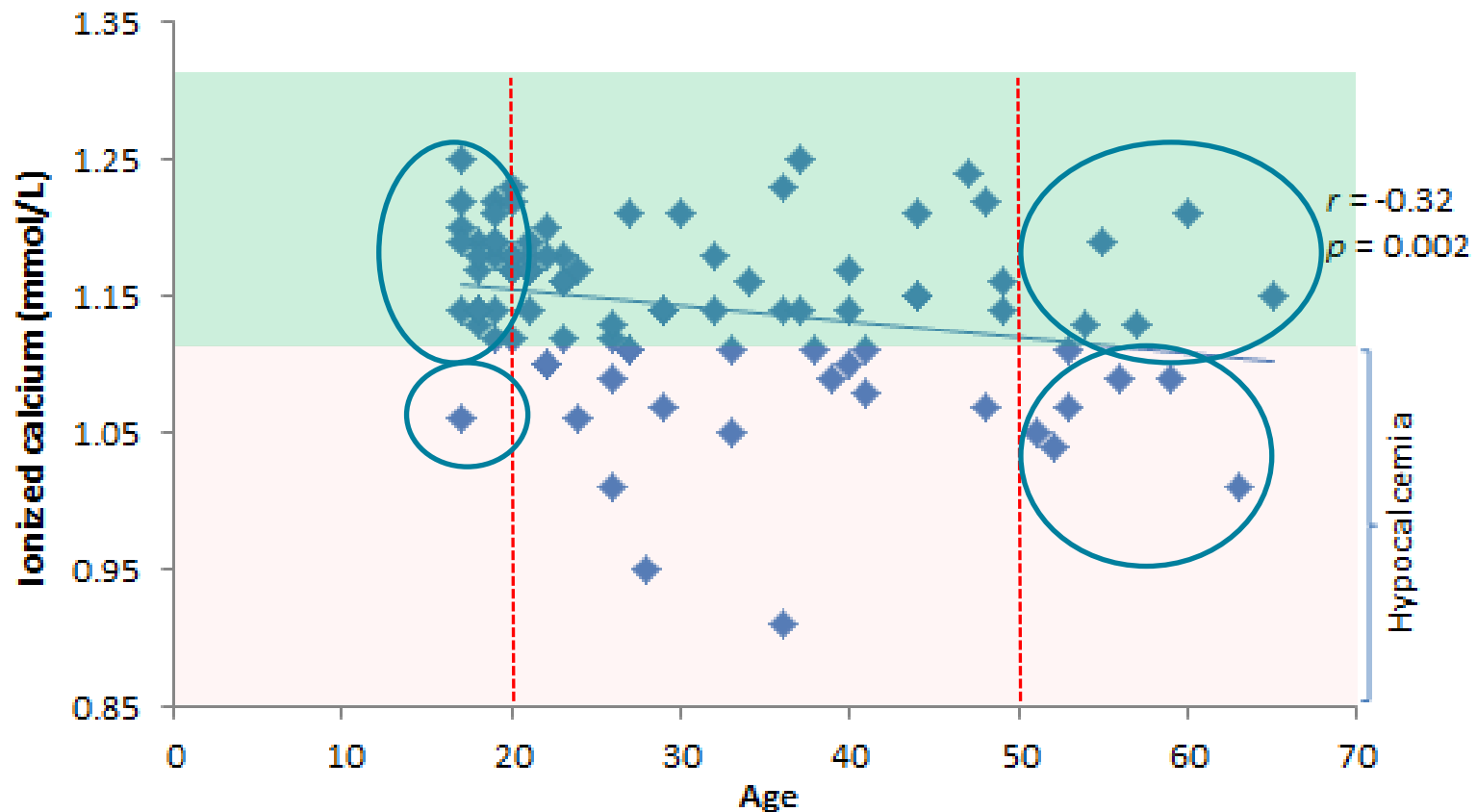
Hypocalcemia:	>50%
Hypothyroidism:	20%
Hyperthyroidism:	5%
Hypomagnesemia:	to be determined
Obesity:	>40%
Type 2 diabetes:	to be determined

Results

pH-corrected ionized calcium

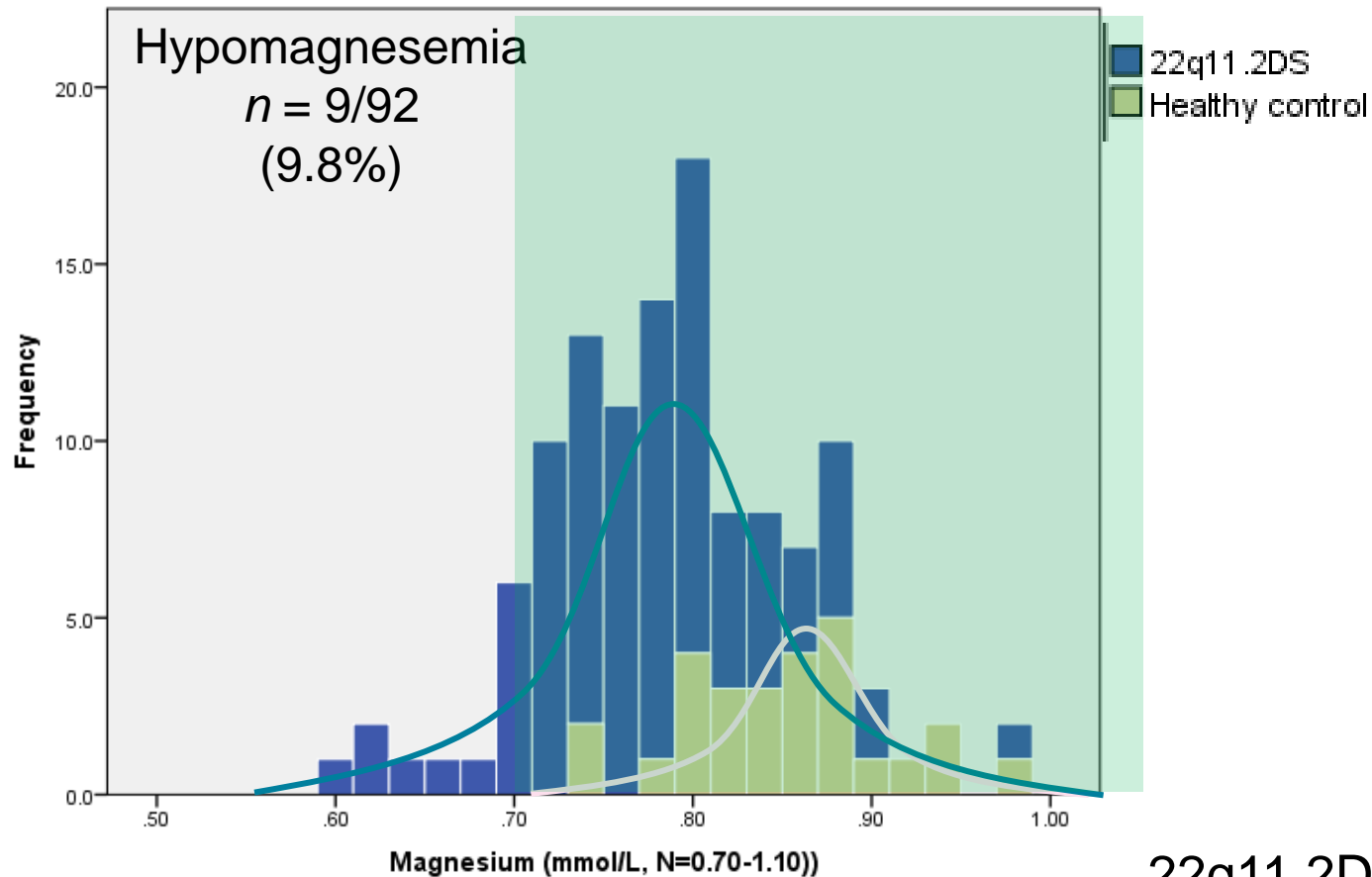


Age effects On calcium levels



Results

Magnesium



$p = 0.000$

22q11.2DS: 0.77 (0.60-0.97)

HC: 0.85 (0.74-0.97)

Obesity



Study in >200 adults with 22q11.2DS vs general population
Average age 26.7 yr

- 43.5% obesity (OR=2.3, CI=1.74-3.02)
- More often in those with antipsychotic drugs (OR=3.88, CI=1.93-7.82)

Endocrinology – management, examples

- Monitoring
 - › Regular bloodwork
 - › Targeted calcium monitoring (e.g., surgery, illness)
- Daily vitamin D supplementation
- Dietary interventions
- Exercise



Endocrinopathies may arise at any age

Skeletal

- Scoliosis: 50%
- Patellar dislocation: 10-20%
- Leg pains



Sleep disturbances

- Sleep apnea
- Disruption of sleep patterns



Sensory impairments

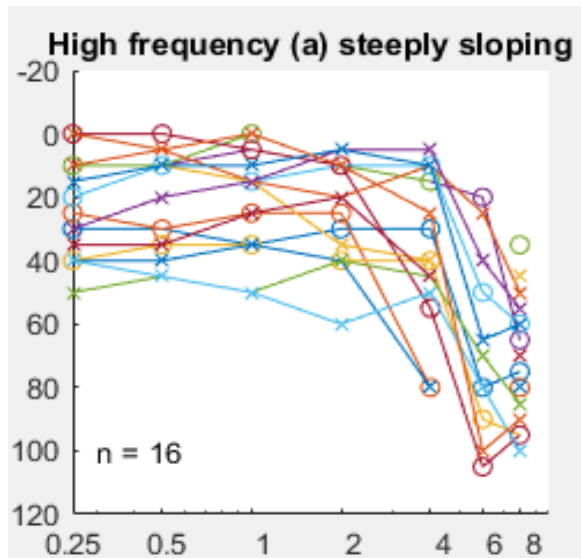
- Impaired sense of smell
- Hearing deficits
- Refraction errors



Hearing loss

➤ Preliminary findings











- › Emma von Scheibler, PhD student
- › In adults at approximately a mean age of 30 years



ORIGINAL ARTICLE

Ocular findings

Ocular findings in 22q11.2 deletion syndrome: A systematic literature review and results of a Dutch multicenter study

Emma N. M. M. von Scheibler^{1,2}  | Emy S. van der Valk Bouman³  |
Myrthe A. Nuijts³  | Noël J. C. Bauer⁴  | Tos T. J. M. Berendschot⁴  |
Pit Vermeltfoort⁵  | Levinus A. Bok⁶  | Agnies M. van Eeghen^{1,7,8}  |
Michiel L. Houben⁹ | Thérèse A. M. J. van Amelsvoort²  | Erik Boot^{1,2,10}  |
Michelle B. van Egmond-Ebbeling³

-  Refractive errors
-  We do not know much about ocular problems in elderly

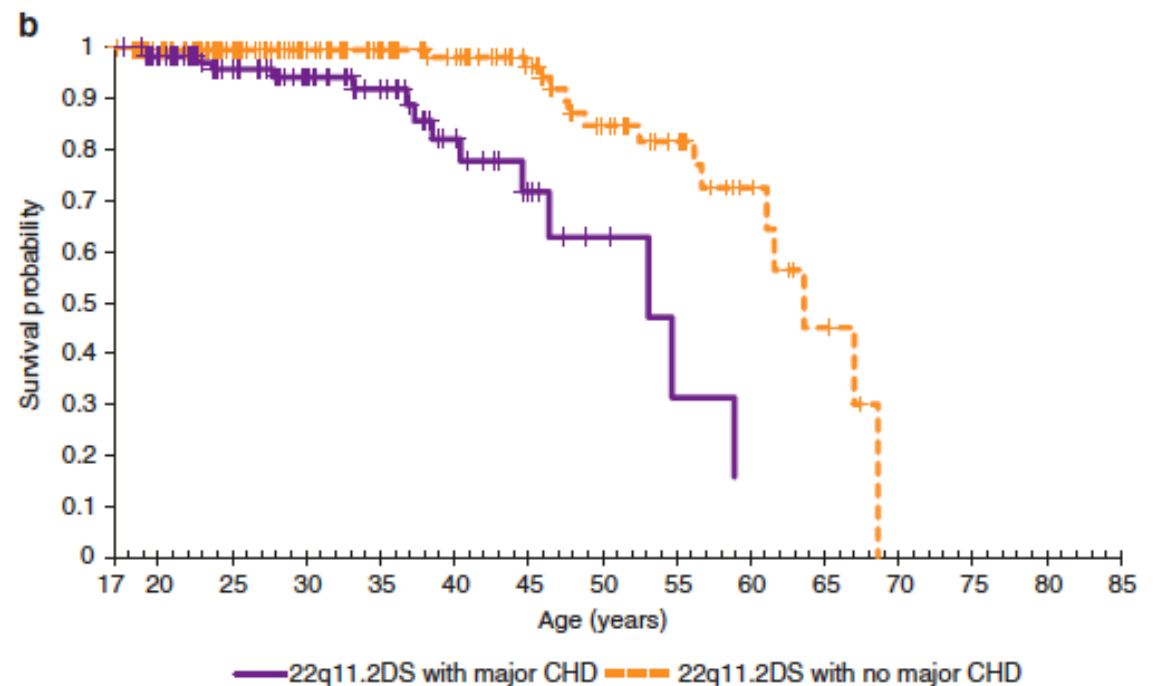
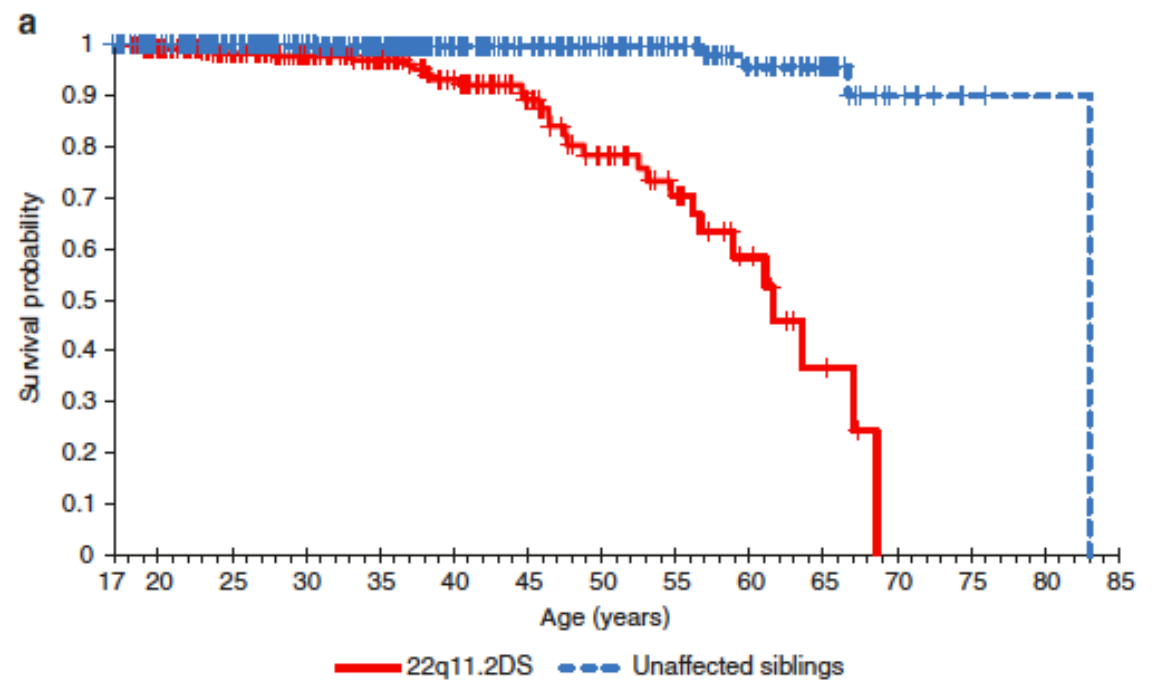
Other, e.g.:

- Fatigue (multiple causes)
- Thrombocytopenia (low platelet count; usually mild)
- Constipation
- Dental issues
- Polypharmacy (≥ 5 medications)

Life expectancy

Mortality

- Probability of survival to age 45 years was
 - › 72% for those with major CHD
 - › 95% for those with no major CHD



Aging in 22q11.2 deletion syndrome

- Multimorbidity (≥ 2 medical conditions)
 - › comparable with those of the general population several decades older
- Age-related conditions, e.g.:
 - › Hearing loss
 - › Obesity
 - › Type 2 diabetes
 - › Parkinsonism
- Reduced life-expectancy compared to unaffected siblings

Key ingredients of effective management

- Goal: optimizing lifetime health and functioning
- Preventive care
- Standard treatment of individual manifestations
 - › There are no 'one fits all' solutions
- Involvement of families and other caregivers
- Seeing the person
- Focus on overall functioning, not just the medical issues
- Often a delicate balance



Effective management, a delicate balance

An example

Non-compliance

Obesity

Psychosis

Hypocalcemia

22q11.2 deletion



Worsen obesity

Treatment of psychosis
(Antipsychotic)

Improve compliance
Risk of *hypercalcemia*

Multidisciplinary approach
Not only medical

Take home message

➤ All adults with 22q11.2DS need follow-up for

- › Recognition
- › Evaluation
- › Surveillance
- › Management
- › Counseling

of possible chronic diseases





erik.boot@sheerenloo.nl