Understanding Mortality Risk in PWS: Lessons from the French National Reference Centre

Dr Gwenaëlle Diene and Pr Maithé Tauber ,

Reference center of Prader-Willi Syndrome

CHU de Toulouse, France

- What do we know about causes of death in PWS?
- Which risks appear most frequently across the lifespan?

- What warning signs may be missed?

- What can families and healthcare professionals do to reduce preventable harm?

Causes of death in Prader-Willi syndrome: lessons from 11 years' experience of a national reference center 2004/2014

Table 2 Causes of death among patients with Prader-Willi syndrome by age

Causes of death	Children < 18 years old ($n = 17$), n (%)	Adults ≥ 18 years old ($n = 87$), n (%)	Total ($n = 104$)
Respiratory cause			55
Respiratory failure[a]	2 (12%)	40 (46%)	
Respiratory infection	4 (23%)	9 (10%)	
Cardiovascular cause			15
Cardiac failure	2 (12%)	6 (8%)	
Pulmonary embolism	0	4 (5%)	
Other cardiovascular causes	2 (12%)	1 (1%)	
Gastrointestinal cause			4
Occlusion	0	3 (3%)	
Acute gastroenteritis	1 (6%)	0	
Severe infection			4
Sepsis	0	2 (2%)	
Other infectious cause	1 (6%)	1 (1%)	
Sudden death	4 (23%)	14 (16%)	18
Other causes	0	3 (3%)	3
Unknown cause	1 (6%)	4 (5%)	5

[a]Significant difference between children and adults, $p = 0.009$

Pacoricona Alfaro et al. Orphanet Journal of Rare Diseases (2019)

Causes of death in Prader-Willi syndrome: 2015-2025

Aim of the study:
- To identify cases
- To determine the causes of death
- To compare with data from 2004–2014

Methodology: 3 sources of information:
Data from the CépiDc national death register
Data from PRADORT centres
Data from the Prader-Willi France association

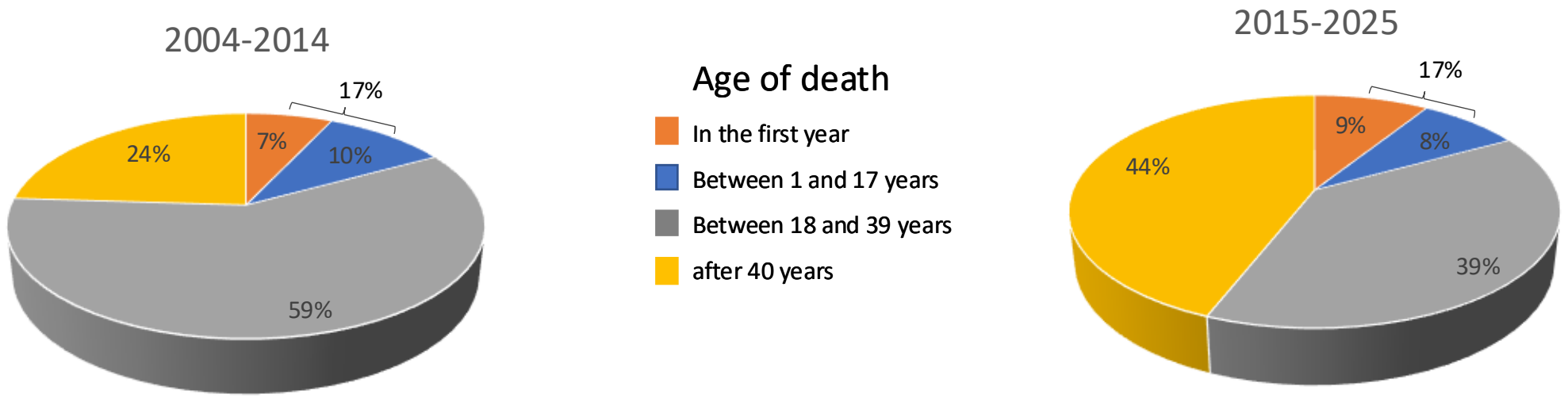
Results:
- 156 cases identified*
- - Median age 36.5 years
- - Between 14 and 15 per year, except for 2022 (28 cases)

**108 cases known to CépiDC, 95 cases known to the CRMR, 46 known cases common to both*
Data for 2025 is missing from the CépiDC register; this will be available in July 2027

Comparison of age at death: 2004–2014 // 2015–2025

Based on the combined known cases from CépiDC and PRADORT (N=156)

	Number of deaths in the first year of life	Number of deaths among people aged between 1 and 18	Number of deaths among people aged between 18 and 39	Number of deaths among people aged 40 and over
2004-2014 (N=105)	8	10	62	25
2015-2025 (N=156)	14	13	61	68



Data available in 95 patients

- **18 children**
- 77 adults

10 deaths in the first year of life

N°/Sex	Genotype	Age of death	Cause
1/M	Disomy	3 weeks	Discontinuation of treatment
2/M	Déletion	3 weeks	Discontinuation of treatment
3/M	Disomy	2 weeks	Discontinuation of treatment
4/M	Disomy	1 month	Discontinuation of treatment
5/F	Deletion	2 weeks	Discontinuation of treatment
6/M	APM	2 months	Sudden death
7/F	Disomy	5 months	Sudden death
8/F	APM	5 months ½	Sudden death
9/M	Deletion	8 months	Infection
10/M	Deletion	1 month	Respiratory failure

8 deaths among children aged between 1 and 18

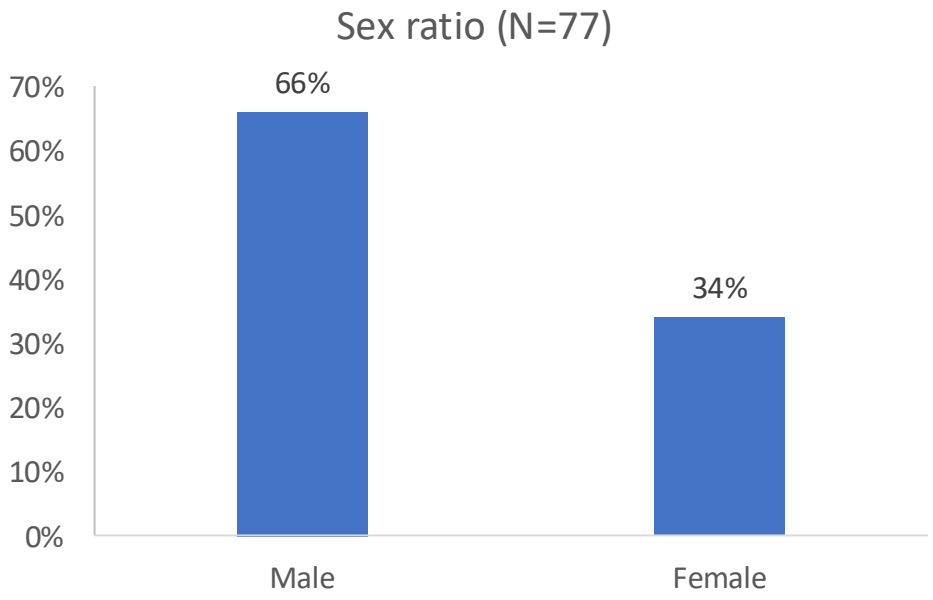
N° /sex	Genetic subtype	Age at death	Cause	Details
1/M	Disomy Down's syndrome	1 year 4 months	Respiratory failure	Refractory hypoxaemia; episodes of PAH
2/M	Disomy	3 years 4 months	Respiratory infection	severe Obesity (Z score IMC + 6 DS)); Respiratory failure due to influenza A; History of obstructive bronchitis and adrenal insufficiency ?
3/M	Disomy Johanson-Blizzard syndrome	3 years 9 months	Gastrointestinal obstruction / malformation	Twisting of the small intestine
4/F	Disomy	10 years 2 months	Chronic myeloid leukaemia	
5/F	Deletion	14 years 8 months	Sepsis following obstructive pyelonephritis	Severe obesity, diabetes
6/M	Deletion	14 years 11 months	Respiratory infection	Severe Obesity; chronic respiratory failure; pseudoneurogenic bladder
7/M	Deletion	15 years 10 months	Sudden death	OSA with NIV; obesity (BMI 44 kg/m²); psychiatric disorders; Died during sleep
8/M	Deletion	15 years 10 months	Sudden death	OSA with NIV; obesity (BMI 47 kg/m²); hiatal hernia surgery in 2018; psychiatric disorders; Died during sleep

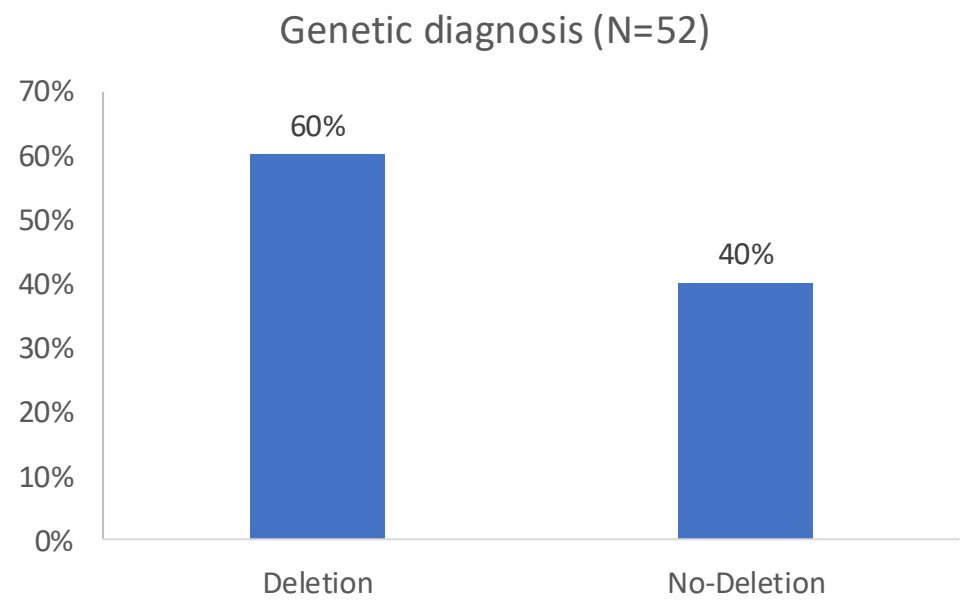
Data available in 95 patients

18 children

77 adults

Data on adults: N=77

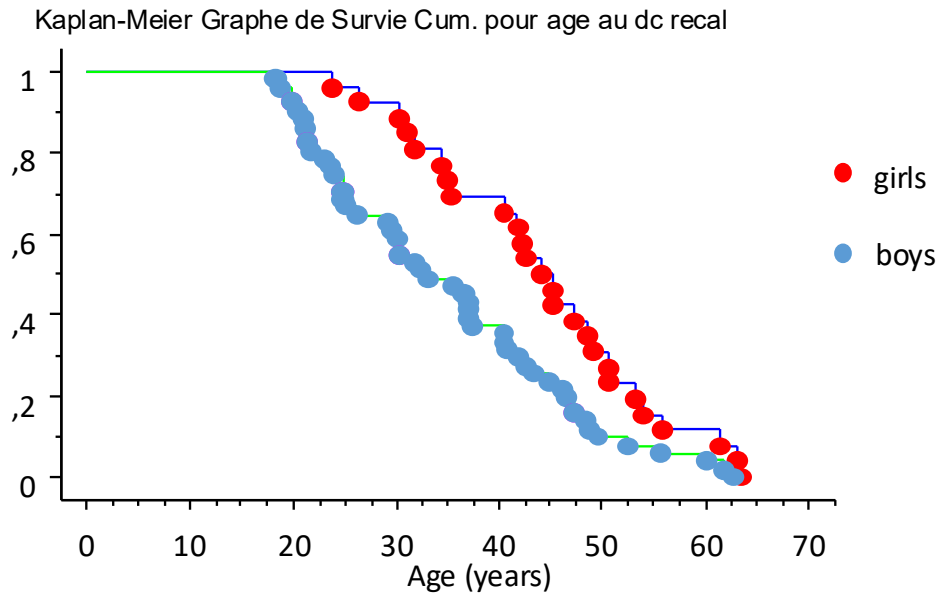




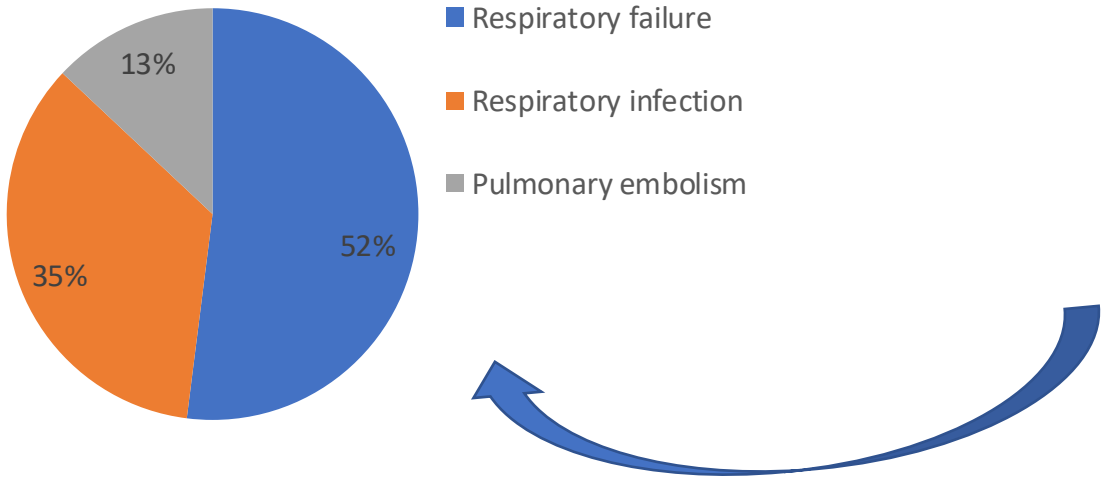
Age at death by gender (N=77)

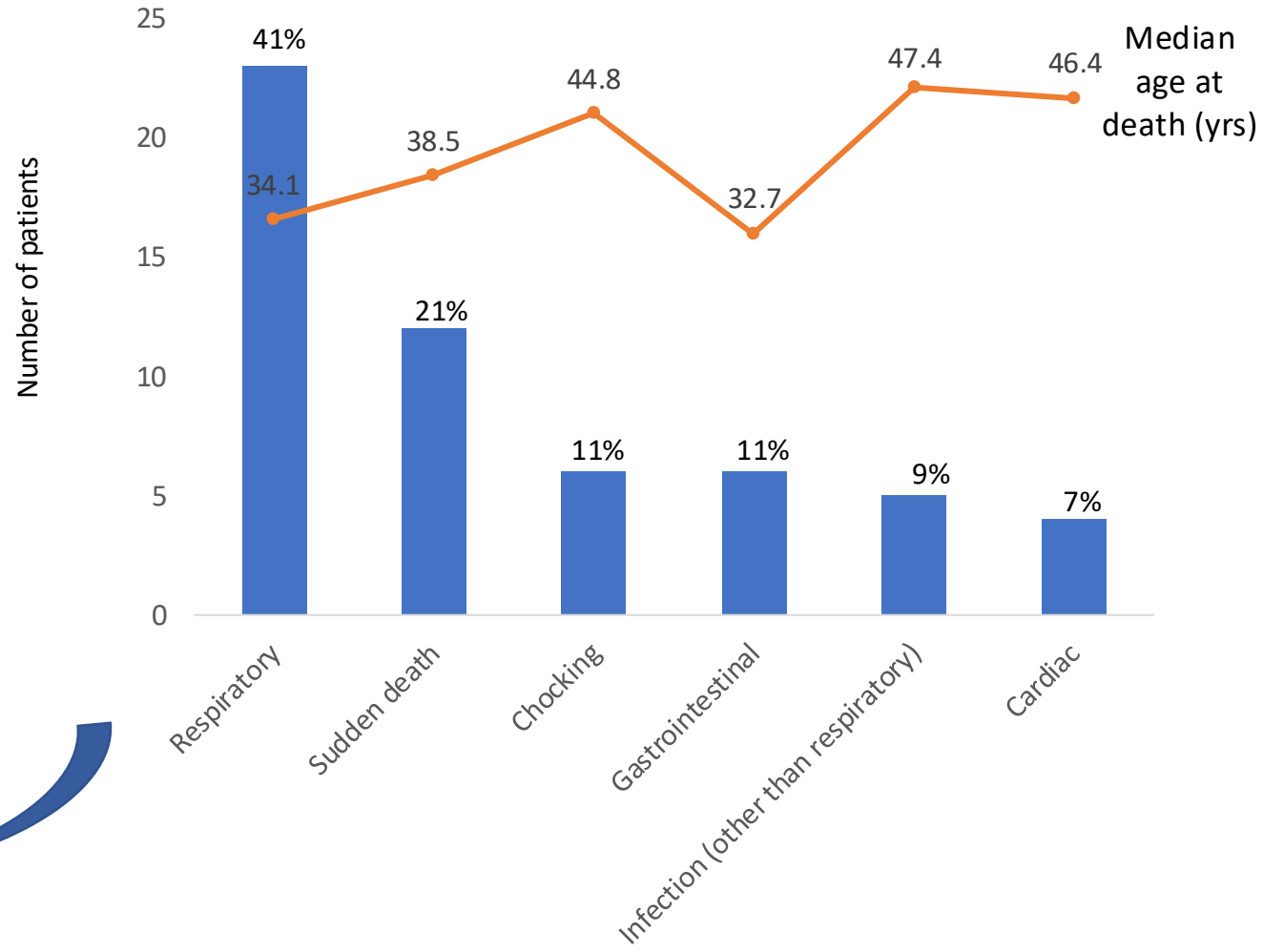
- ✓ Median age at death: 37.2 years
- ✓ The group of boys had a lower median age at death than the group of girls:

  33.1 years versus 44.7 years (p = 0.002)
- ✓ Kaplan-Meier analysis of age by gender:



Causes of death (N = 57)





Comorbidities in adults

- **Obesity in 48/55 patients (87%);** median BMI = 50 kg/m^2 (N=25)
- **OSA in 34/44 patients (77%),** no machine compliance in 21% of cases
- **Chronic respiratory failure in 22/47 patients (47%)**
- **Diabetes in 24/50 patients (48%)**
- Circulatory troubles in 15/44 patients (34%)
- HBP in 10/44 patients (23%)

- What warning signs may be missed?

- **IN CHILDREN <1 YEAR**

✓ withdrawal of treatment following an ethics review

✓ sudden and unexplained infant death syndrome

- **IN CHILDREN AND ADULTS**

- Prevent obesity and extreme obesity

➢ Hypoventilation

➢ sleep apnea syndrome

➢ with subsequent arterial pulmonary hypertension and right ventricular failure

- What can families and healthcare professionals do to reduce preventable harm?

Carefull follow-up and regular evaluations

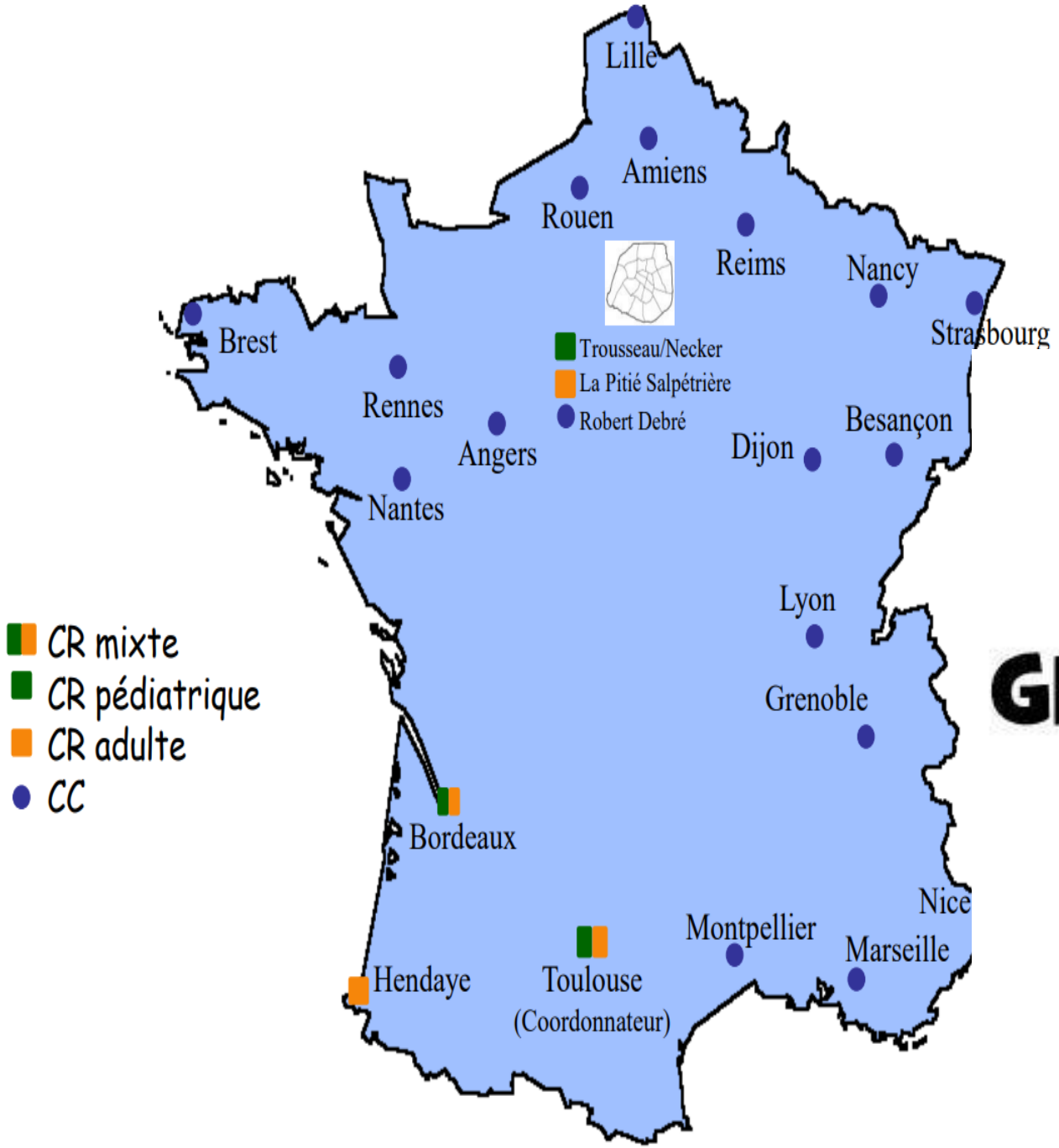
Treatment adherence and confidence in carers

Explain to parents the importance of weight management and how to prevent obesity

Very early polysomnography evaluation and often to treat sleep apnea syndrome if necessary

More cardiac evaluation

Pellikaan et al frontiers in Endocrinology, March 2023


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