

Down Syndrom in Newborns with Congenital Hypothyroidism: A Cross-Sectional Analysis of Data from Trisomy Newborns

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<https://dx.doi.org/10.13005/bpj/3475>

(Received: 30 March 2026; accepted: 18 May 2026)

Down syndrome newborns often have abnormal levels of thyroid hormones, requiring systematic screening for congenital hypothyroidism (HC) if untreated, which can lead to stunted growth and cognitive deficits. A better understanding of the links between Down syndrome and HC is essential to improve care and quality of life for those affected. This study examined the records of 108 trisomy newborns between January 2013 and December 2023, comparing 33 cases with trisomy 21 with HC to 75 trisomy controls without HC. Data included risk factors such as sex, environment, maternal age, birth weight, term of pregnancy, date of delivery, and associated malformations. The analysis was performed with Epi Info, using statistical methods with a p-value < 0.05 considered significant. The results highlight the importance of increased clinical attention for children with Down syndrome, especially in CH. Factors such as seasonality, namely winter season [OR= 3.63 (1.47-8.91)] and spring season [OR= 3.41 (1.34-8.66)], consanguinity [OR= 11.2(4.20-30.24)], prematurity [OR= 4.2 (1.75- 10.31)], Advanced maternal age [OR= 4.42 (1.83-10.6)] and heart defects [OR= 3.41 (1.34- 8.66)] may increase the risk of HC in these newborns. It is essential to consider these factors to prevent this pathology in this vulnerable population better. These findings reinforce our understanding of the issues related to Down syndrome and CH. Several factors contribute to the development of CH in Down syndrome newborns. A multidimensional approach is essential for better understanding these mechanisms and for improving prenatal care and counseling strategies.

Keywords: Congenital hypothyroidism; Consanguinity; Prematurity;
Risk factor; Seasonality; Trisomy 21.

People with trisomy 21, given the genetic abnormalities and physiological factors associated with this condition, are at increased risk of developing various health complications, including endocrine disorders such as hypothyroidism, which affects nearly 50% of Down syndrome adults over their lifetime.^{1,2} About one in four children and more than one in two adults with Down

syndrome will develop thyroid disease during their lifetime, highlighting the importance of regular screening and proper management to preserve their development and improve their quality of life.³

Trisomy infants often have lower thyroxine (T4) levels and higher thyrostimulin (TSH) levels compared to non-trisomy infants,⁴ which highlights the need for systematic screening

of congenital hypothyroidism (CH), which is defined as an endocrine disorder that manifests itself in inadequate production of thyroid hormones at birth, affecting approximately 1 in 2000 to 1 in 4000 newborns.⁵ The causes may be related to either thyroid dysgenesis (ectopia, lack, or failure of thyroid development) or dyshormonogenesis (failure in one of the stages of thyroid hormone biosynthesis).⁶

If CH is not diagnosed and treated early, it can lead to significant growth retardation and cognitive impairment, especially as the incidence of persistent primary CH in infants with Down syndrome is estimated at 1 out of 141; this represents a risk 28 times higher than in the general newborn population.⁷ For example, a 1998 longitudinal descriptive study (Uppsala) of the thyroid function of 85 trisomy children followed up to age 25 reported 35% hypothyroidism.⁸ It is therefore essential to track and know the specific characteristics of the disease and treat it properly. A thorough understanding of these conditions is crucial to preserving the developmental potential of people with Down syndrome and ensuring a better quality of life.⁷

Although trisomy 21 does not directly cause HC, it increases the risk of developing this condition due to genetic and physiological factors. It is therefore crucial that children with Down syndrome are regularly monitored for thyroid disorders to ensure proper care.

Hence, the relevance of in-depth studies relating the relationship between trisomy 21 and HC to understanding the specificities of these conditions in the Moroccan context by taking into account genetic, physiological, and environmental factors.

Investment in research could not only help in clarifying the underlying mechanisms of this predisposition but also in developing more effective screening and treatment strategies, thus improving the quality of life of those affected.

MATERIALS AND METHODS

Study type and environment

This retrospective study involved the records of newborns treated from January 2013 to December 2023. A case-control study on newborns

with Down syndrome diagnosed with CH (cases) matched to newborns with Down syndrome without CH (controls) at the neonatal unit of the Children's Hospital of Rabat's UH, according to the criteria of sex and environment.

Inclusion and exclusion criteria

Only newborns recruited at the neonatal department of the Rabat children's hospital with a diagnosis of T21 confirmed and having benefited from the measures of TSH and T4 during the neonatal period were included. Infants with incomplete records or other non-trisomy-related birth defects were excluded.

Ethical statement

Institutional Ethics Committee (CERB) of Mohammed 5 Rabat University (reference 41/25) has undertaken a study after approval

Variables studied

Data collected with records included risk factors likely to promote HC in T21, including the mother's age, parity, and date of birth. The route of delivery, the sex of the newborn, gestational age, birth weight, Apgar score at 5 minutes, psychomotor development and stature-weight, and the presence of congenital heart defects and/or thyroid and/or gastrointestinal malformations were also recorded.

Each case was matched to 1, 2, or 3 controls. Finally, 16 cases were matched with 48 controls, 10 series with 20 controls, and 7 series with 7 controls, according to sex and environment criteria. The total population studied is 108 newborns.

Statistical analysis

After data collection, we used the Epi Info software version 7.2.6.0 to perform the various tests, namely the descriptive statistics to describe the population characteristics. The bivariate analysis allowed us to assess exposure risk by comparing maternal characteristics and variables of case newborns with those of controls using the chi-square test, considering a value of $p < 0.05$ as statistically significant.

Finally, multivariate analysis was performed for factors with statistical differences between the study groups to evaluate the difference explained by the different variables, expressed in odds ratio (OR) adjusted, with their respective 95% confidence intervals (CI).

RESULTS

To enhance the stages of selecting our target population for this study, we have developed a flow chart. This visual tool helps to clarify and organize the different phases of the process, thus facilitating the understanding of the criteria and uses in our research approach. (Fig.1)

Description of the population under study according to matching criteria

Out of 108 participants in this study, 33 newborns with T21 and CH (cases) were matched

to 75 newborns with T21 without CH (controls) based on sex and environment. Of the 33 cases, 22 were female (67%) and 11 were male (33%). As for the controls, 50 were female (67%) and 25 male (33%). 73% of the cases and 69% of the controls were from urban areas (Table 1).

Characteristics of the target population of the study

For parity, 33% of cases and 31% of controls have less than 2 children, 45% of cases and 41% of controls have between 2 and 5 children, and 22% of cases and 28% of controls have more

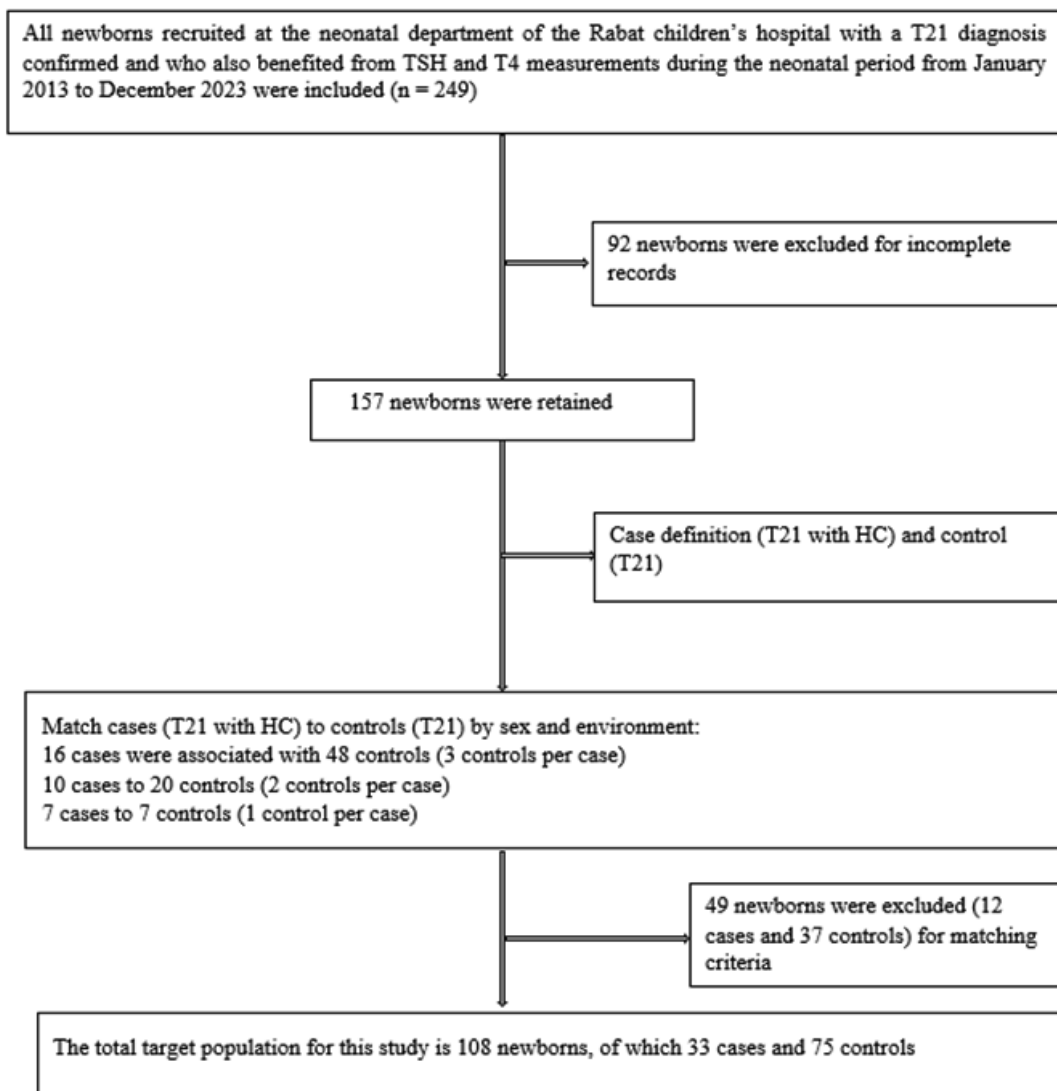


Fig. 1. Flow chart of target population selection for the study

than 5 children. The relation between parity and the presence or absence of CH in trisomy patients is insignificant.

For pregnancy follow-up, 21% of cases followed their pregnancy against 41% of controls, while 36% of cases and 59% of controls did not. A significant relationship was found between pregnancy follow-up and the presence of CH ($p < 0.05$).

Normal delivery was observed in 33% of cases and 44% of controls, while 67% of cases

and 57% of controls were delivered by caesarean section. The relationship between delivery mode and CH development is insignificant.

Apgar score is <7 in 33% of cases and 56% of controls, and >7 in 67% of cases and 44% of controls, showing a significant relationship between the Apgar score and the presence or absence of CH in people with Down syndrome.

Birth weight between 1500 g and 1999 g was raised in 49% of cases and 25% of controls, and 42% of cases and 22% of controls between

Table 1. Description of the population studied

Variables	Cases (n=33)		Controls (n=75)		X ² (P value)	statistical significance
	Size	Percent	Size	Percent		
Gender						
Female	22	67%	50	67%	00 (1.00)	N.S[1]
Male	11	33%	25	33%	00 (1.00)	N.S
Area						
Urban	24	73%	52	69%	0.12 (0.72)	N.S
Rural	9	27%	23	31%	0.12 (0.72)	N.S

Table 2. Characteristics of the population studied

Variables	Cases N=33 (n) %		Controls N=75 (n) %		p
Parity					
<2	(11)	33%	(23)	31%	NS ¹
[2-5]	(15)	45%	(31)	41%	
>5	(7)	22%	(21)	28%	
Pregnancy follow-up					
Yes	(21)	64%	(31)	41%	<0.05
No	(12)	36%	(44)	59%	
mode of delivery					
Normal	(11)	33%	(33)	44%	NS
Cesarean section	(22)	67%	(42)	56%	
Apgar score 5 min					
<7	(11)	33%	(42)	56%	<0.05
>7	(22)	67%	(33)	44%	
Birth weight					
]1500- 1999]	(16)	49%	(18)	25%	<0.05
[2000- 2499]	(14)	42%	(16)	22%	
[2500- 2999]	(1)	3%	(22)	27%	
[3000- 3499]	(1)	3%	(10)	14%	NS
[3500- 4000[	(1)	3%	(9)	12%	
Delayed psychomotor development					
<2 years	(5)	15%	(28)	37%	<0.05
[2- 5 years]	(8)	24%	(40)	53%	
>5 years	(20)	61%	(10)	13%	

Table 3. The bivariate analysis of the main factors related to HC in trisomy 21

Variables Significance	Cases (n=33) Size %	Controls (n=75) Size %	X ² (P value)	OR (IC at 95%)	Statistical
Season					
Winter	15	14	8.37 (0.003)	3.63 (1.47- 8.91)	High SS ¹
Spring	13	12	7.05 (0.0079)	3.41 (1.34- 8.66)	High SS
Summer	3	29	9.61 (0.0019)	0.15 (0.04- 0.56)	Low SS ²
Autumn	2	20	5.99 (0.014)	0.17 (0.03- 0.81)	Low SS
Consanguinity	20	9	27.5 (0.00000015)	11.2 (4.20-30.24)	High SS
Term of pregnancy					
Preterm	17	15	10.91(0.00095323)	4.2 (1.75- 10.31)	High SS
Full-term	16	60	10.91(0.00095)	0.39 (0.23- 0.68)	Low SS
Maternal age					
<30 years	2	0	4.63 (0.031)	-	N.S
[30-40 ans]	18	16	11.71(0.00061)	4.42 (1.83-10.6)	High SS
>40 years		59	15.90(0.00066)	0.17 (0.02- 0.42)	Low SS
Congenital heart malformation	13	12	7.05 (0.0079)	3.41 (1.34- 8.66)	High SS

2000 g and 2499 g. A significant relationship was noted between birth weights < 2999 g and the development of CH. 15% of cases and 37% of controls have a developmental delay before 2 years, 24% of cases and 53% of controls between 2 and 5 years, and 61% of cases and 13% of controls after 5 years. A significant relationship was observed ($p < 0.05$). (Table 2)

The bivariate analysis of the main determinants

Our study showed a significant relationship between the birth season of Down syndrome infants and the presence of CH. Of the 33 cases examined, 15 newborns, or 45%, were born in winter, while 13 cases, representing 34%, were born in the spring. For the control group, 14 individuals, or 18%, were born in winter and 12, or 16%, in spring ($p < 0.05$). The risk of developing the disease in newborns with Down syndrome in winter and spring is more than 3 times higher.

Consanguinity, which refers to marriage and reproduction between individuals with close kinship links such as cousins, was observed in 61% of newborns with trisomy HC, versus 12% without trisomy CH ($p < 0.05$). The risk of developing CH was 11.2 times higher compared to those without any notion of consanguinity.

The present study shows that CH is statistically significantly related to prematurity ($p < 0.05$), with a 4.2 times higher risk of developing HC than those born at term.

The mean maternal age was 38 ± 2 years for cases vs 42 ± 2 years for controls. The 30 to 40 age group is the most prevalent, with 55% of cases and 21% of controls, while almost 40% of cases and 79% of controls are in the over 40 age group ($p < 0.05$). Our result showed that 6% of cases had the HC's cause a hypotrophy of the thyroid gland at birth by thyroid ultrasound. (Table 3)

DISCUSSION

This study aims to analyze the determinants related to CH in people with Down syndrome. By collecting the transcribed data on the records, we are looking to clarify the implications of these comorbidities, which could thus improve the management and follow-up of these vulnerable patients. To this end, it is essential to recognize the various determinants of this predisposition to develop appropriate screening and

monitoring strategies, ensuring early and effective management of thyroid disorders in children with Down syndrome.

The main determinants related to HC in trisomy

Thus, our study has highlighted several main determinants, including seasonality, consanguinity, pregnancy term, and maternal age.

The seasonality

45% of newborns with Down syndrome, 21 with CH (cases), were born in winter, while 34% were born in spring. In the control group, 18% were born in winter and 16% in spring ($p < 0.05$). The risk is higher at 3.63 (1.47-8.91) times to develop HC in Down syndrome in those born in winter and 3.41 (1.34-8.66) in spring.

Our study confirms the literature, because Abbasi et Harrari (2022) highlight the significant association between winter and CH⁹. Similarly, the study by Hall et al. (1999) examines the incidence of CH on seasonality in the West Midlands, England, concluding that there is a significant relationship, particularly during winter and spring¹⁰.

This variable may be crucial in the development of CH in newborns with trisomy 21. In winter, iodine deficiency, particularly in low-iodine regions, increases the risk of CH, as iodine is essential for thyroid hormone synthesis. In addition, winter is marked by respiratory infections affecting maternal health and fetal development.⁶ In spring, dietary variations may influence nutrient intake, such as iodine and selenium, while increased seasonal allergies may also impact maternal health and fetal development as a result.⁹ This analysis highlights environmental factors often overlooked in the development of CH in Down syndrome infants. Iodine deficiency, especially in winter, is a concern and highlights the importance of adequate nutrition. In addition, seasonal infections and allergies show how maternal health is interlinked with fetal health, requiring special attention during these periods.

The consanguinity

In our study, 61% of Down syndrome infants with consanguinity developed CH ($p < 0.05$); the risk of developing CH is 11 times higher in people with Down syndrome who have consanguinity.

Several studies have confirmed our findings. One by Hall and Hutchesson (1999) reveals a potential link between consanguinity

and increased CH cases in the West Midlands, England, and the combination of consanguinity and Down syndrome can increase the risk of thyroid dysfunction.¹⁰ G. Allen et al. point out that Infants with Down syndrome have an increased risk of CH, with a 26-fold incidence compared to the general population.¹¹

Consanguinity is, therefore, a major risk factor for the development of genetic disorders, as it increases the likelihood of transmitting recessive alleles that may contribute to chromosomal abnormalities.

Maternal age

Our research results state that the average maternal age for cases is 38 ± 2.6 years, while it is 42 ± 2.2 years for controls. Age analysis shows that 55% of cases and 21% of controls are in the 30-40 year age group, with a risk of 4.42 (1.83-10.6) times to develop CH, demonstrating a strong statistical relationship between the [30-40] age group in mothers giving birth to Down's disease and the presence of CH. Those born to mothers over 40 years old have a risk of 0.17 (0.02- 0.42), which shows a weak statistical relationship with maternal age of more than 40 years, giving birth to trisomy and the presence of CH.

Several studies show that the risk of trisomy 21 increases with age, reaching about 1 in 128 for mothers aged 40.¹¹ The study by Zhou (2020) identifies perinatal risk factors associated with CH in a retrospective cohort in China, highlighting significant associations with maternal age.¹²

Hakim (2022) examines risk factors in Iran and reveals correlations between maternal age and CH incidence, highlighting the importance of increased awareness and early detection to improve health outcomes.¹³ In addition, the study by Zhang (2018) shows that maternal age significantly influences levels of thyroid-stimulating hormone (TSH) in newborns in a prospective cohort in China.¹⁴

This research highlights the significant impact of maternal age on CH risk in Down syndrome newborns. The results highlight the importance of increased awareness for women over 30, who should be given careful medical follow-up. In addition, promoting early screening is crucial to improving health outcomes for these vulnerable newborns.

The term of pregnancy

Our study also shows that the presence of CH in Down syndrome newborns is linked to increased rates of preterm births, with a 4.2 (1.75-10.31) times higher risk of developing CH.

Premature births are more common in children with Down syndrome than in the general population. Studies show that trisomy have an increased risk of obstetric complications, which can lead to early births.¹⁵ A study by Zhou (2020) highlights significant associations between the pregnancy term and CH in a retrospective cohort in China.¹⁴ Similarly, Hakim (2022) reveals a correlation between the term of pregnancy and the incidence of CH in southwestern Iran, highlighting the importance of increased awareness and early detection.¹²

It is a concern that Down syndrome infants are more likely to be born prematurely, which highlights the importance of enhanced medical surveillance. The studies result highlight the need for early detection to anticipate and manage potential complications. Increased awareness could help improve health outcomes for these vulnerable newborns.

Heart defects

In our research, 40% of the cases had a heart malformation with a 3.41 (1.34- 8.66) times higher risk of developing CH, indicating a high statistical significance among trisomy with heart malformations associated with CH.

Congenital heart defects affect about 40 to 50% of individuals with trisomy 21, including anomalies such as the atrioventricular canal and septal defects. HC is also more common in this population, with an incidence 26 times higher than in the general population¹⁶. The study by Iqbal and Schimer (2007) highlights the importance of monitoring thyroid function in cardiac patients to better understand interactions between thyroid health and cardiac performance.¹⁷

These results highlight the importance of early detection and appropriate medical follow-up. Given the link between thyroid hormones and neurological development, it is essential to integrate thyroid monitoring into the care of patients with Down syndrome. A better understanding of these interactions could improve interventions and outcomes for these vulnerable children.

The delay of psychomotor development

Our research also found that all cases and controls developed a psychomotor developmental delay ($p < 0.05$). Delayed psychomotor development is common in individuals with trisomy 21, and about 50% of these individuals have thyroid disorders, including CH. This condition, often underdiagnosed, can aggravate neurological deficits due to the importance of thyroid hormones in central nervous system maturation.¹⁸

These results highlight the importance of early detection and appropriate medical follow-up. Given the link between thyroid hormones and neurological development, it is essential to integrate thyroid monitoring into the care of patients with Down syndrome. A better understanding of these interactions could improve interventions and outcomes for these vulnerable children.

In summary, our study confirmed the critical importance of clinical care for children with Down syndrome, especially with CH. Several factors, such as seasonality, consanguinity, prematurity, advanced maternal age, and congenital heart defects, can significantly influence the risk of developing this pathology in Down syndrome newborns. This association reinforces the validity of the conclusions drawn and suggests significant implications for the understanding of the phenomena studied.

Study limitations

This study has certain limitations, including a lack of available data on parity and socio-economic levels, and the absence of prior similar studies in this specific region for comparison.

In addition, the non-self-reporting nature of the case-control study restricted the ability to supplement certain information with interviews with parents in the target population, limiting the depth of data collected. It is also important to note that the specificity of rare diseases such as CH requires a long-term approach.

However, these limitations do not alter the scientific relevance of this research, and the results obtained can be used as a basis for developing a policy to raise awareness and systematically screen HC while considering socio-economic considerations.

CONCLUSION

This study highlights the importance of special clinical attention for children with Down syndrome, especially regarding CH. It highlights several crucial determinants that influence the risk of developing this pathology.

Among the known pedagogical aspects, it is recognized that the link between maternal age and the risk of trisomy 21 intensifies with age, especially after 30 years. In addition, consanguinity history is a major risk factor for genetic disorders, including Down syndrome. Finally, it is well established that newborns with Down syndrome are more likely to be born prematurely, which increases their risk of complications such as CH. In addition, research demonstrates a strong correlation between the presence of heart defects and the increased risk of HC in newborns with Down syndrome. Finally, she points out that all the cases studied presented a delay in psychomotor development, thus accentuating the need for early thyroid monitoring.

However, this study also reveals innovative elements. It highlights the significant impact of seasonality on the development of CH in trisomy, highlighting often-overlooked environmental influences.

ACKNOWLEDGMENTS

The authors sincerely thank all the healthcare professionals who support this study. Their valuable insights and time were instrumental to its success.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not Applicable

Author Contributions

Boumehti Boutaina: Conceptualization, Data collection, Methodology, analysis, Writing – Original Draft; Mochhoury Latifa: Data Collection, Methodology, Analysis; Iaziji Lamy: Analysis, Visualization; Barkat Amina: Visualization, Supervision; Chebabe Milouda, Visualization, Supervision.

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