

# Congenital Hypothyroidism: Reduction in the Female to Male Ratio Following the Decrease of the TSH Cut-off Point Used for Neonatal Screening

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## Background knowledge

Since the initiation of neonatal screening-programs for Congenital Hypothyroidism (CH) in the 1970's, an increase in the incidence of CH has been observed worldwide. This change has been attributed to the gradual use of lower TSH cut-offs that lead to the detection of milder cases of CH. Based on currently used screening cut-offs, CH occurs in approximately 1:2,000 to 1:4,000 newborns, varying by geographic location and ethnicity. A female predominance, approaching a 2:1 female to male ratio, has been consistently reported.

The **National Greek Neonatal CH screening program** was initiated in 1980 and is carried out by a **single laboratory** that receives and tests the Guthrie cards from all maternity hospitals. The program initially covered the Athens Metropolitan and suburban area but quickly expanded and covered the entire country. Over the last 35 years, more than **3,690,000 neonates** have been screened.

## Objective and hypothesis

To assess whether the gradual decrease in the TSH cut-off limits has affected the female to male ratio in neonates with CH.

## Patients and Methods

The annual records from 1980 to 2014 of the Greek Neonatal CH screening program were thoroughly reviewed. For each year, the TSH cut-off point was recorded and the percentage of female and male neonates with CH was calculated.

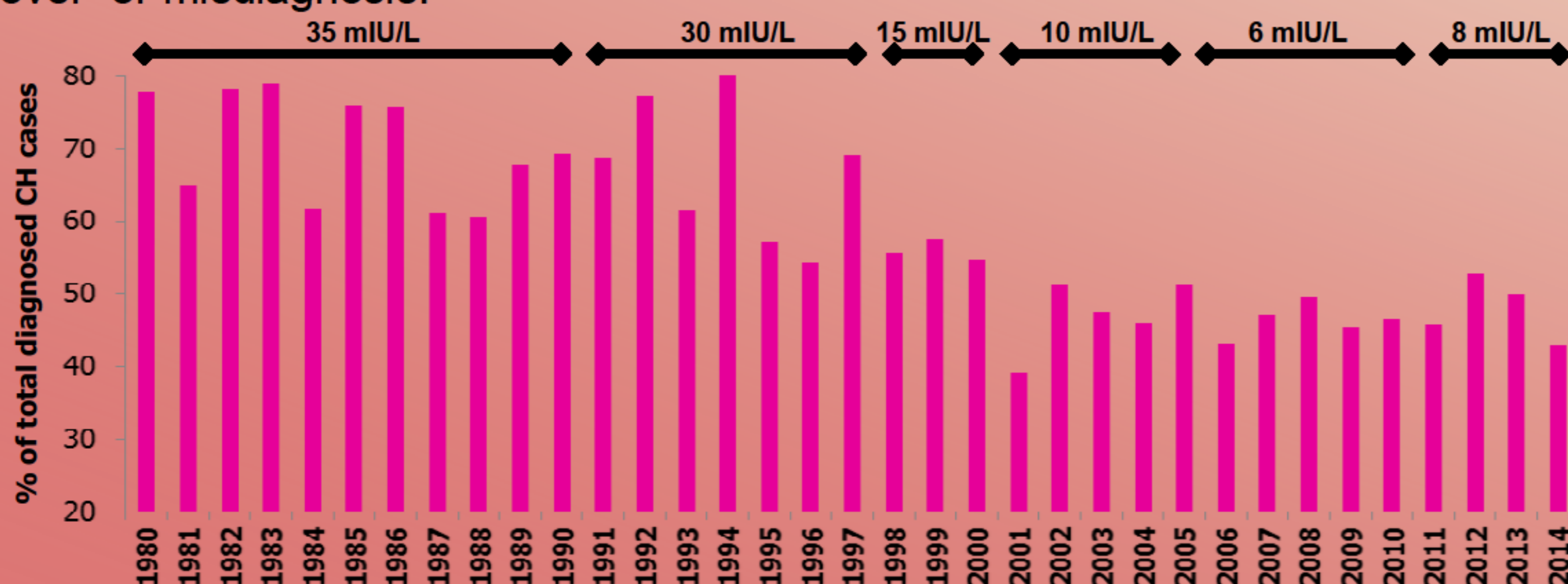
## Results and Discussion

The TSH cut-off point was gradually lowered from 35 mIU/L in 1980 to 6 mIU/L in 2006 and moved back to 8 mIU/L as of 2012. The proportion of female neonates diagnosed with CH was 78% of the total CH cases in 1980 but showed a progressive decrease to lower than 50% in the last decade. In fact, the use of a 6 to 8 mIU/L TSH cut-off point consistently leads to a marginal male predominance (**Figure 1**).

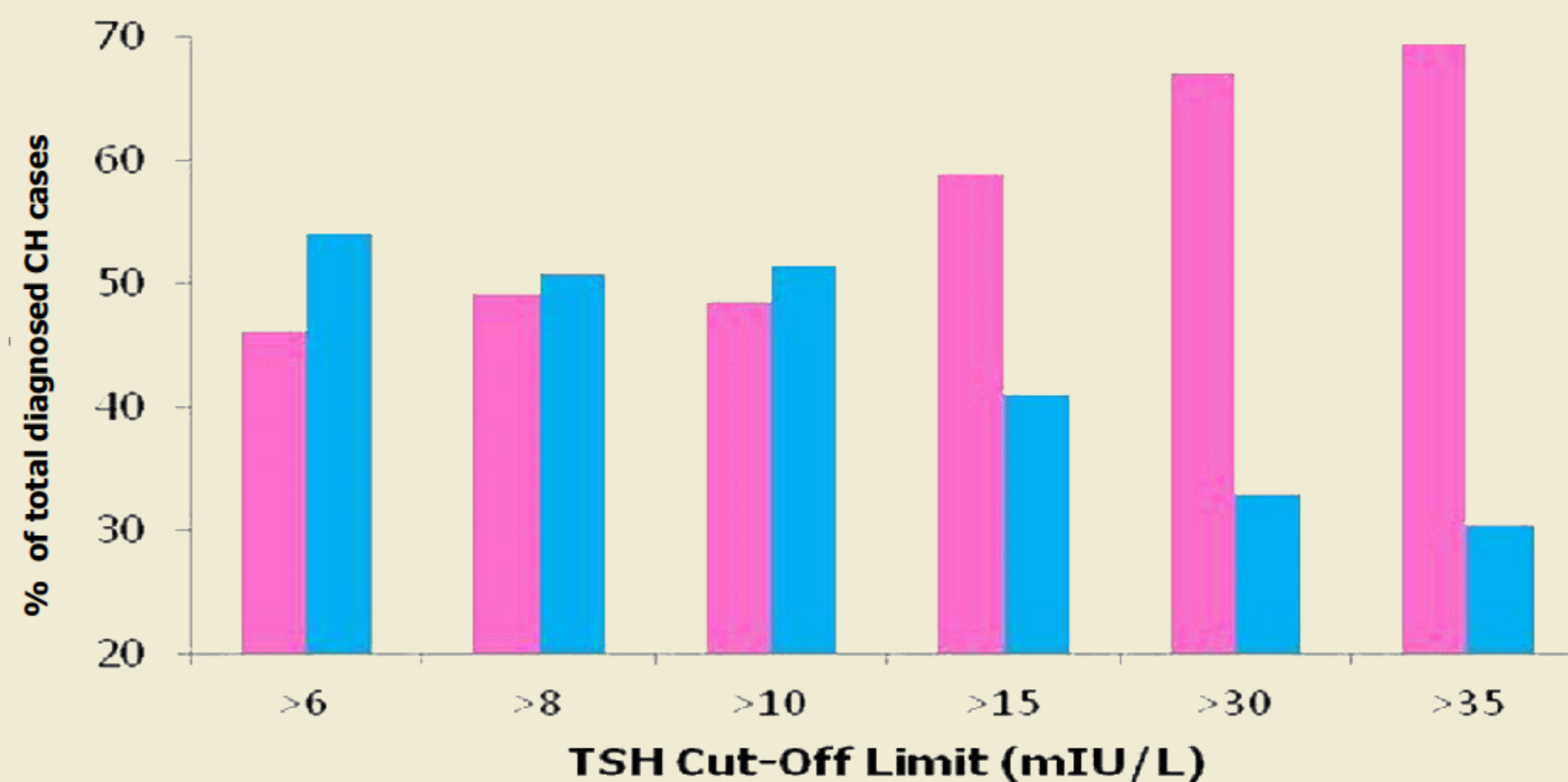
The data from all the calendar years that share the same TSH cut-off limit (6, 8, 10, 15, 30 and 35 mIU/L) were grouped together. A progressive increase of the female percent was evident when moving from the 6 mIU/L to the 35 mIU/L cut-off limit. The reverse trend was observed with respect to boys. The impact of the TSH threshold limit on the Female to Male ratio is apparent (**Figure 2**).

The various TSH cut-off limits that have been used from 1980-2014 (6, 8, 10, 15, 30 and 35 mIU/L) were "applied" to the neonates born in 2014, the number of newborns that would theoretically be detected was noted and the percentage of girls was calculated for each one of the groups. This theoretical percentage of females with CH (born in 2014) was compared to the historical data of the last 35 years for each TSH cut-off limit and seems to fully correspond. Therefore, the decrease in the female percent within the CH population may be attributed to the reduction of the TSH cut-off limit rather than another factor altering the disease prevalence in a gender dimorphic manner. (**Figure 3**).

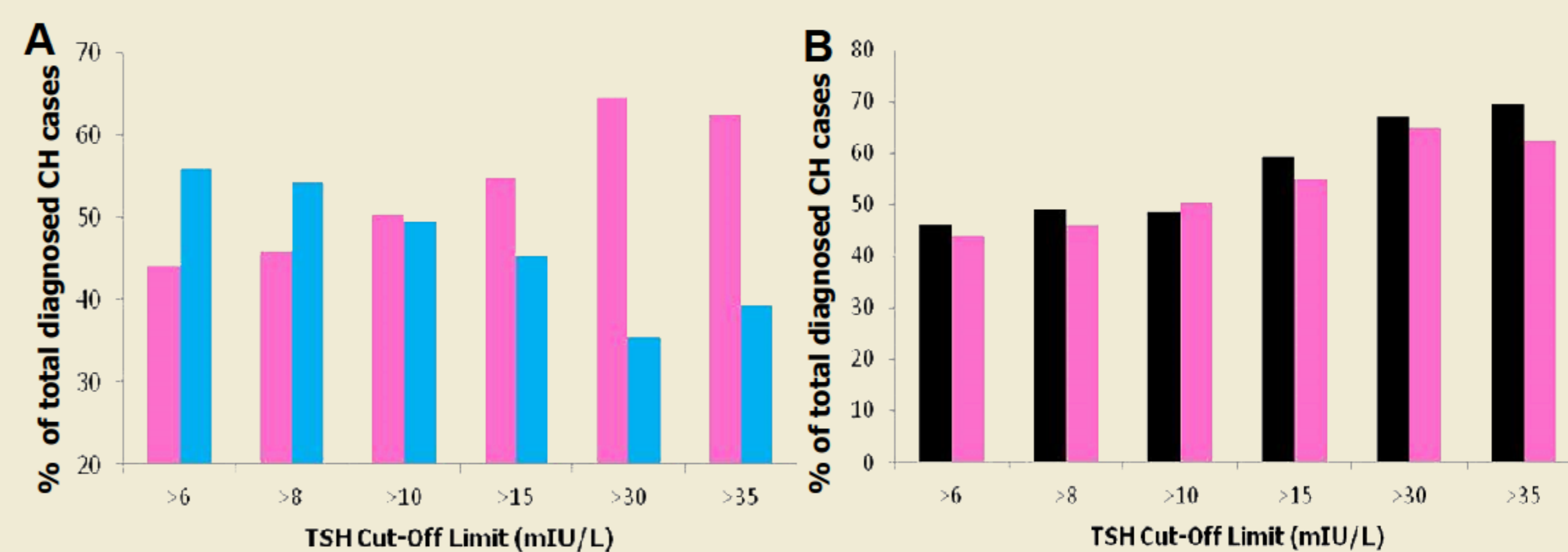
Lowering of the TSH cut-off limit uncovers an increased number of CH patients. Long-term follow up (~50%) and phone interviews of neonates born in 2009 (TSH cut-off limit 6 mIU/L, n=224, now age 6 yrs) reveals that the majority of patients was still on LT4 substitution therapy, even those diagnosed with a TSH level in the Guthrie card <10 mIU/L as shown in **Table 1** and **Figure 4**. Low TSH cut-off limits reveal milder but nevertheless real CH cases. Therefore, the change in the female to male ratio due to the reduction of the TSH cut-off limit may not be attributed to over- or misdiagnosis.



**Figure 1:** Data from the Greek Neonatal CH screening program including more than 3,690,000 neonates. The proportion of females diagnosed with CH with respect to the total number of newly diagnosed neonates for each calendar year from 1980 (girls: 78%) until 2014 (girls: 43%) is depicted. A progressive decrease to less than 50% is observed in the last decade leading to a marginal male predominance. The corresponding TSH screening cut-off limits that were applied each year are depicted on top.



**Figure 2:** The percent of female (pink) and male (blue) neonates diagnosed with CH within the last 35 years (from 1980 until 2014) through the Greek Neonatal CH screening program is depicted. Data from all the calendar years that share the same TSH cut-off limit were grouped together. A progressive increase of the female percent is evident when moving from the 6 mIU/L to the 35 mIU/L cut-off limit. The reverse trend is observed with respect to boys. The impact of the TSH threshold limit on the Female to Male ratio is apparent.



**Figure 3:** (A) Theoretical percent of female (pink) and male (blue) neonates that would have been diagnosed if the various TSH cut-off limits used from 1980-2014 (6, 8, 10, 15, 30 and 35 mIU/L) were "applied" to the neonates born in 2014 (B) The theoretical percentage of females (pink) with CH (born in 2014) was compared to the historical data (black) of the last 35 years for each TSH cut-off limit and seems to fully correspond. Therefore, the decrease in the female percent within the CH population may be attributed to the reduction of the TSH cut-off limit rather than another factor altering the disease prevalence in a gender dimorphic manner.

TSH	Gender	Patients	No treatment in 2015
<10	females	60	18 30 %
	males	90	38 42 %
10-30	females	24	10 42 %
	males	19	5 26 %
>30	females	19	1 5 %
	males	12	3 25 %

**Patients diagnosed in 2009 using a TSH cut-off limit of 6 mIU/L. Table 1:** Long-term follow up (~50%) and phone interviews reveals that the minority of these patients (n=224) that are now 6 yrs old have discontinued LT4 substitution therapy. This applies even to patients diagnosed with a TSH level in the Guthrie card <10 mIU/L. **Figure 4:** The overall percent of CH patients (females and males) that have discontinued LT4 substitution therapy (transient CH) with respect to the TSH in the Guthrie card is depicted.

## Comments and Conclusions

Change of the TSH cut-off point used in the neonatal CH screening program alters the female to male ratio. Specifically, lowering of the TSH limit results in a decrease of female percentage among neonates with CH. When a 6 to 8 mIU/L TSH cut-off point is applied, an inversion of the female to male ratio is observed and male preponderance is consistently noted. When the various TSH cut-off limits (6, 8, 10, 15, 30 and 35 mIU/L) that have been used from 1980-2014 are "applied" to the neonates born in a given year the same female to male ratios are consistently found. Low TSH cut-off limits reveal milder but nevertheless real CH cases as shown by the permanent CH cases diagnosed even when using the 6 mIU/L limit. Therefore, the change in the female to male ratio associated with the reduction of the TSH cut-off limit does not seem to be a result of over- or misdiagnosis. In severe CH cases females predominate but this is not true for milder cases since males constitute the majority of cases.

