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ORIGINAL ARTICLE

Hypothyroidism and perchlorate: an ecological study of hypothyroidism in the Maltese Islands

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Background

One of the lesser-known causes of hypothyroidism is perchlorate exposure, a by-product of fireworks. Recent studies in the Maltese islands showed increased concentration of perchlorate in dust fall, leading to public concerns about its health effects. This study aims to examine the hypothyroidism trends in the resident Maltese population and assess for a link with perchlorate exposure.

Methods

A retrospective ecological study using laboratory and population data was carried out to calculate the crude and direct age-standardised incidence rates of hypothyroidism in the resident population.

Results

Significantly lower overall age-standardised incidence rates for hypothyroidism were found in the region of Gozo; however no clearly discernible geographical pattern of hypothyroidism with clear potential link to perchlorate exposure was found.

Conclusion

The lower hypothyroid incidence rates in Gozo warrant a comparative study to establish whether this difference is attributable to differing levels of perchlorate exposure from different scale of firework use.

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Hypothyroidism is a common endocrine disorder worldwide[1], with overt hypothyroidism affecting between 0.2% and 5.3% of the general population in Europe.[2] The commonest cause of primary hypothyroidism worldwide is iodine imbalance related to dietary intake.[3] A less well-known cause is exposure to perchlorate, which is a powerful oxidising agent used commercially for propellants, in food packaging and fireworks. Human exposure to perchlorate occurs via dust inhalation and ingestion of contaminated food and water.[4]

Perchlorate is a strong competitive inhibitor of iodine for the sodium-iodide symporter (NIS)[5,6], resulting in inhibition of thyroid hormone production and consequent increase in thyroid stimulating hormone (TSH) release as homeostatic mechanisms fail.[5,7] Although the effect of perchlorate on health is largely negligible and reversible due to the small amounts produced in the natural state[8], exposure to environmental perchlorate contamination from anthropogenic sources is internationally acknowledged as a potential cause of clinical and sub-clinical hypothyroidism.[9]

Malta has a land area of 246km^2 and a population of 442,978 whereas Gozo is smaller with a land area of 67km^2 and a population of 32,723.[10] The islands are dependent on imported goods for over 75% of food consumption, resulting in the importation of considerable quantities of packaged foods[11], and also have widespread use of fireworks for celebrations during village feasts during the summer months. Recent environmental studies on perchlorate fallout from fireworks in Malta have fuelled concerns among the general public on the potential negative effects on health.[12] These studies have revealed significantly elevated levels of perchlorate in both atmospheric and indoor dust[4,12] which in some areas were above the recommended limits as determined by the European Food Safety Authority.[13] In another study carried out by Pace & Vella[14], perchlorate was also found to be above the detection limit in 44% of groundwater samples tested, 62% of runoff samples collected during the first storms after summer, and in 42 – 89% of tap water samples tested in three sampling sessions. This study also showed that the levels in drinking water were low but persistent.[14]

Until now, there have not been any studies, in Malta or abroad, examining the association between perchlorate exposure from fireworks fallout and hypothyroidism. Furthermore, the incidence rate of sub-clinical and clinical hypothyroidism in the Maltese population has never been analysed over time and by geographical location. This research gap has precluded researchers from attempting to identify potential associations between perchlorate exposure and health outcomes.

This study aims to investigate the reported incidence of clinical and sub-clinical hypothyroidism in the Maltese population across time and by geographical locality as a first step in identifying any potential associations between perchlorate exposure and hypothyroidism in Malta.

MATERIALS AND METHODS

A retrospective ecological study was carried out to study the trends in hypothyroidism in the Maltese resident population in Malta and Gozo between 2009 and 2017. Secondary data on the state of thyroid function was obtained from the Pathology Department of Mater Dei Hospital (MDH) in the form of results of thyroid function tests (TFTs) from routine or clinically indicated blood testing for the years 2008 to 2017, both years included. Population demographic details were procured from the National Statistics Office (NSO). General data protection regulations (GDPR) procedures were followed during the extraction of the secondary data.

MDH is the principal acute state hospital of the islands, and its Pathology Department processes the majority of blood testing nationwide. Since the Maltese health system provides universal health coverage, only a minority of Maltese residents make use of private laboratories.[15] Thus, the TFT results provided by the MDH Pathology Department accounted for the vast majority of thyroid function testing in Malta and were considered to be a good proxy for national trends in hypothyroidism for this study by the authors. The dataset provided included pseudonymised case identification numbers, gender, locality of residence, TSH result, and the date when the blood sample was taken.

A case definition for a ‘new hypothyroid case’ was developed in line with the aim of this study. A case was defined as a person with a high TSH result of more than 3.0micIU/ml at any time in a given year provided that the same person was not identified as a case by the same definition in any of the preceding years under study. Since the study aimed to investigate a potential association between perchlorate exposure and hypothyroidism, the inclusion of both clinical and subclinical forms of hypothyroidism in the case definition was important, since perchlorate exposure is associated with both forms.

Table 1 *Number of Abnormally High TSH results defined as TSH results of more than 3micIU/ml, after applying exclusion criteria. *Abbreviation: TSH = Thyroid Stimulating Hormone*

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017
total tests	77,200	95,281	123,048	140,073	161,962	181,906	194,823	213,841	220,321
no numerical result	471	2,140	6,637	5,201	2,897	3,125	3,953	4,202	5,243
no Hospital ID	116	104	126	659	122	142	239	280	270
TSH* results <3.0 micIU/mL	64,135	78,781	94,413	110,000	130,487	146,813	157,942	176,472	182,903
TSH results >3.0 micIU/L	12,478	14,255	21,872	24,213	28,456	31,826	32,689	32,887	31,905

Records with incomplete TSH data, lacking case identification numbers, or with missing age or locality details were removed. Following this, all records of presumably normal or high thyroid function, denoted as records with a TSH result of less than 3.0micIU/ml, were removed as they did not fit in the case definition (Table 1), while abnormally high TSH results of persons that were identified as cases in preceding years were excluded on the premise that such results did not serve to qualify a person as a new case. Cases aged "0" were removed to exclude neonates from analysis as congenital hypothyroid screening generates large numbers of false-positive results which would have disproportionately skewed the results[16] (Table 2). Assuming that those with previously diagnosed clinical or subclinical hypothyroidism submit to testing at least once a year, and providing that data was only available since the 1st of January 2008, only data between 2009 and 2017 was used for further analysis. Data for 2008 was used to filter new cases from established cases from 2009 onwards, as it contained a mixture of new and established cases which could not be distinguished from each other without the availability of thyroid function data prior to 2008. The dataset for 2008 was thus inadequate for further analysis.

The demographic data provided by the NSO included the total Maltese population by NUTS (Nomenclature of Territorial Units for Statistics) region and locality, in single years of age and according to gender for the years 2009 – 2017.[10] This data was used as denominator to calculate crude and age-standardised

Table 2 *Number of new hypothyroid cases by year. A new hypothyroid case is defined as a person with an abnormally high TSH result of more than 3.0micIU/ml at any time in a given year provided that the same person was not identified as a case by the same definition in any of the preceding years under study. Cases aged "0" were removed to exclude neonates from analysis as congenital hypothyroid screening generates large numbers of false-positive results which would have disproportionately skewed the results. *Abbreviation: TSH = Thyroid Stimulating Hormone*

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	Grand Total
TSH* results >3.0 micIU/L	12,478	14,255	21,872	24,213	28,456	31,826	32,689	32,887	31,905	230,581
new Hypothyroid cases	6,023	5,723	8,732	8,573	9,089	9,099	8,556	7,761	6,917	70,473
aases aged 0 years	191	221	538	565	629	645	669	667	554	4,679
new Hypothyroid cases excluding cases aged 0	5,832	5,502	8,194	8,008	8,460	8,454	7,887	7,094	6,363	65,794
	12,478	14,255	21,872	24,213	28,456	31,826	32,689	32,887	31,905	

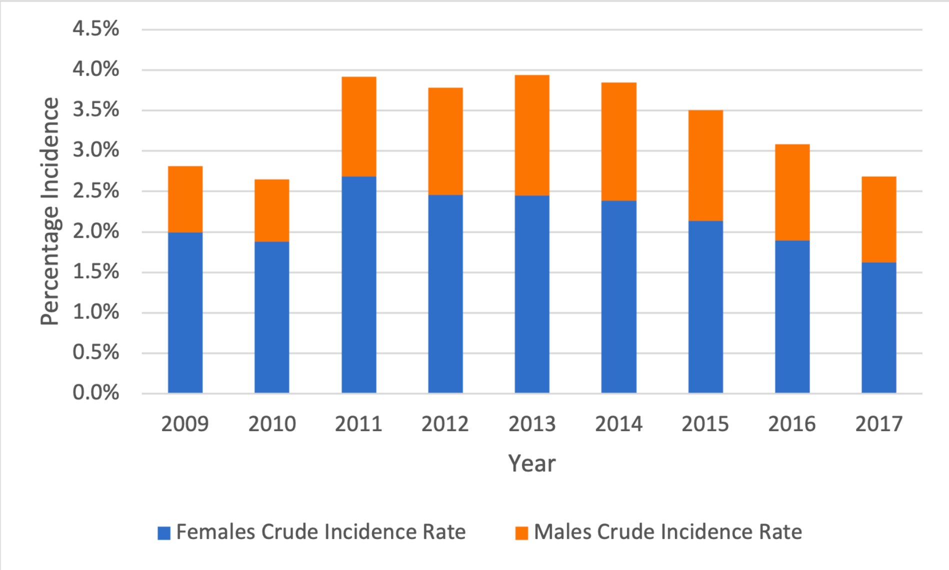

Figure 1 *Crude incidence rate of hypothyroidism per year according to gender between 2009 and 2017. A hypothyroid case is defined as a person with an abnormally high TSH result of more than 3.0micIU/ml at any time in a given year provided that the same person was not identified as a case by the same definition in any of the preceding years under study.*

incidence rates for hypothyroid cases by gender and locality using Microsoft Excel. The direct age-standardisation technique was applied on a modified World Health Organisation (WHO) standardisation template for males and females.[17] For age-standardisation, the Maltese population data for 2013 was used as the reference denominator population as it represented the mid-point population between 2009 and 2017. Since population by single year of age was not available at locality level, the demographic structure of each locality was assumed to follow the same overall demographic structure of the respective NUTS region. On this assumption, the regional demographic structure was used in the reference population in the computational method for age-standardisation per locality. Stata statistical software[18] was used to carry out Poisson regression analysis that helped identify differences between the incidence of hypothyroidism among regions and localities.

RESULTS

The average reported crude incidence rate of new hypothyroid cases, as per case definition, for the years 2009 - 2017 was 1.7 per 100 persons (%) per year. For the years 2009-2017, females had an overall higher average crude incidence rate than males, with 2.33% and 1.34% per year respectively (Figure 1). The average crude incidence rate of hypothyroidism was observed to increase with age (Figure 2).

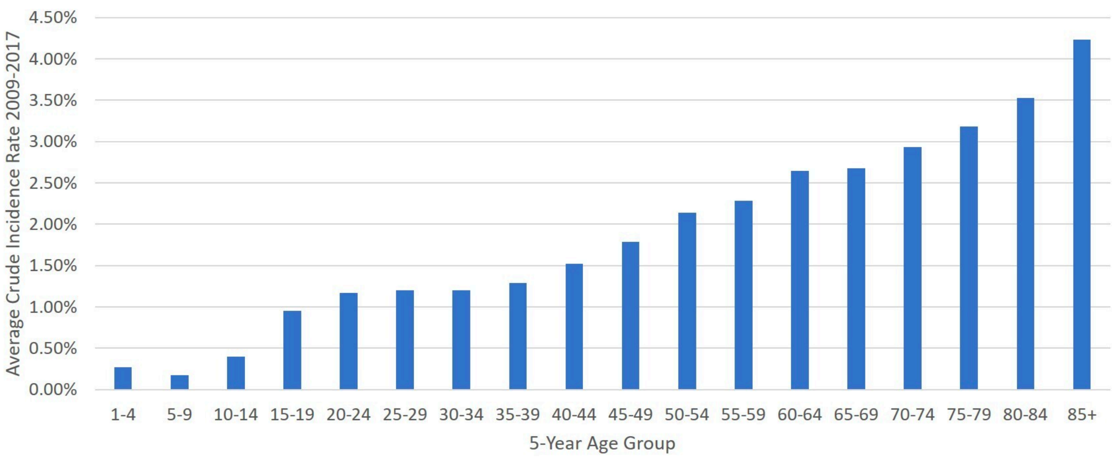

Figure 2 *Average crude incidence rate of hypothyroidism by 5-year age group for the years 2009-2017 for cases 1 year and older. A hypothyroid case is defined as a person with an abnormally high Thyroid TSH result of more than 3.0micIU/ml at any time in a given year provided that the same person was not identified as a case by the same definition in any of the preceding years under study.*

Table 3 *Incidence rate of hypothyroidism per 100,000 population and Annual Crude Incidence Rate per 100,000 population per District according to Gender. A hypothyroid case is defined as a person with an abnormally high TSH result of more than 3.0micIU/ml at any time in a given year provided that the same person was not identified as a case by the same definition in any of the preceding years under study.*

District	Males				Females			
	Average annual number of new cases per year	District population	Annual crude incidence rate per 100,000 population	Age-standardised incidence rate of Hypothyroidism	Average annual number of new cases	District population	Annual crude incidence rate per 100,000 population	Age-standardised incidence rate of Hypothyroidism
Southern Harbour	528	39,589	1,333.70	1,425.02	926	39,883	2,321.79	2,356.96
Northern Harbour	728	63,091	1,153.89	1,255.24	1,378	63,889	2,156.87	2,217.28
South Eastern	380	34,035	1,116.50	1,330.14	677	32,438	2,087.06	2,315.9
Western	379	29,207	1,297.63	1,446.92	680	29,629	2,295.05	2,413.78
Northern	425	32,983	1,288.54	1,476.12	748	33,224	2,251.38	2,466.85
Gozo & Comino	169	1,5628	1,080.39	1,172.91	291	15,828	1,838.51	1,883.03

Average crude incidence rate of hypothyroidism by 5-year age group for the years 2009-2017 for cases 1 year and older. A hypothyroid case is defined as a person with an abnormally high Thyroid TSH result of more than 3.0micIU/ml at any time in a given year provided that the same person was not identified as a case by the same definition in any of the preceding years under study.

The results obtained after age-standardisation according to gender provided comparison between incidence rates at regional and locality level. Males and females showed a similar pattern with regards to the age-standardised incidence rates of hypothyroidism by NUTS district, with populations residing in the Western and Northern districts showing the highest rates whereas those living in Gozo having the lowest rates (Table 3).

Statistical testing for differences by NUTS districts showed that both genders living in Gozo had significantly (p<0.05) lower rates of hypothyroidism than other districts. Age-standardised rates for localities (Annex 1) did not provide a definitive pattern or a clearly discernible trend of hypothyroidism incidence by locality. However, significantly lower rates (p<0.05) were obtained for males in Swieqi and San Gwann, and for females in Paola, Pembroke and Swieqi (Figures 3 and 4).

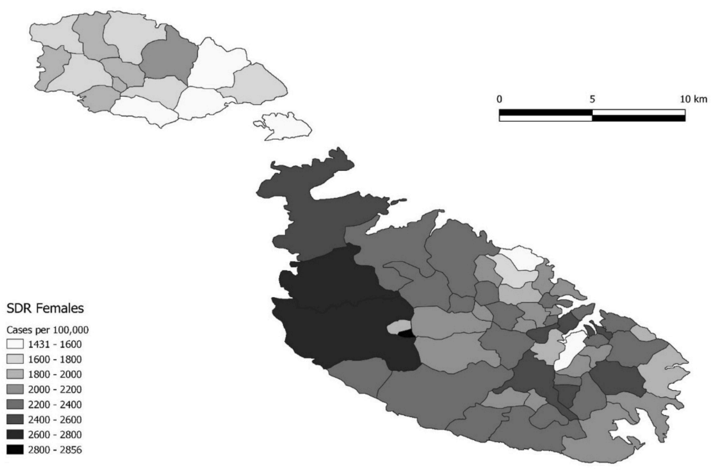

Figure 3 *Age-Standardised Incidence rate of Hypothyroidism for Females for the year 2013*

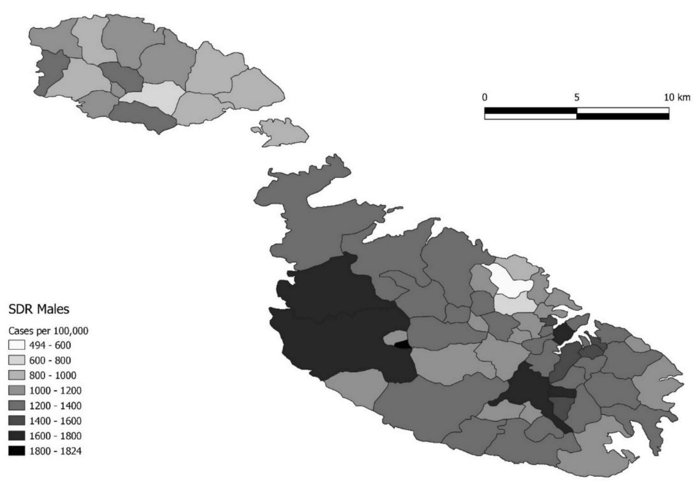

Figure 4 *Age-Standardised Incidence rate of Hypothyroidism for Males for the year 2013*

DISCUSSION

The general trends of the findings in this study are in agreement with the results of other similar studies, with a higher incidence of hypothyroidism found in women[19] and with increasing age[1,20],.[21] Studies have shown that these trends reflect the increased prevalence of anti-thyroid antibodies (ATA) in women and older persons. ATA are positively associated with elevated TSH levels[1,19,20], and their prevalence in the general population can be as much as 10%.[22]

The slight overall increase in incidence of hypothyroidism over the 9-year period observed in this study was in agreement with a retrospective study carried out in Scotland to investigate the changing trends in thyroid disorders, which attributed this to the increase in the number of tests performed leading to improved detection rates.[23] In Malta, family doctors were given access to request free-of-charge TFT testing at the Pathology Department of MDH as from 2012.[15] This change in policy is reflected in the spike in incidence noted at around this time.

Internationally, geographical variation in the incidence and prevalence of hypothyroidism has been associated with variable iodine intake, as small differences in intake result in relatively large effects on the thyroid function[24],.[25] Although the scale of the geographical variation is usually recorded over larger geographical areas, this current ecological study similarly exposed variations in the incidence of hypothyroidism in different localities and areas of the Maltese islands which might be associated with iodine intake in the diet. There is no published local data about the state of iodine intake in the Maltese islands to date.[26] However, an unpublished study focusing on the iodine status of the healthy Maltese population carried out in 2013 found that 53% of the healthy population (n=134) had deficient iodine levels.[27] This study did not find any significant differences by gender or amongst different age-groups, and the researchers did not investigate regional differences. However, dietary differences between the two main islands might account for the generally lower incidence of high TSH levels found in Gozo. Further studies about differences in regional blood iodine levels are needed to investigate whether iodine intake is a determinant for the lower incidence of hypothyroidism in Gozo.

The link between perchlorate levels and the incidence of hypothyroidism in Malta has not been studied previously. The studies that were carried out investigated the levels of perchlorate in dust fall[4] and in different sources of potable water.[14] These two factors, together with exposure from ingestion of contaminated food, are the three main pathways via which perchlorate might influence the development of hypothyroidism in the Maltese population.

Dust inhalation is primarily influenced by the prevailing North-Western wind that affects the distribution of settled dust contaminated with perchlorate, leading to higher concentrations in the South-Eastern region of the islands.[4] On the other hand, patterns resulting from ingestion of contaminated food and water are less defined. Perchlorate present in groundwater is diluted once this is mixed with desalinated water before distribution to households.[14] Furthermore, fruit and vegetables produced locally that might be contaminated with perchlorate are distributed across the island, minimising the regional effect of any perchlorate present. There is no information on the rates of consumption of local fruits and vegetables by locality across the Maltese islands.

The age-standardised patterns of reported hypothyroidism incidence obtained in this study were not concordant with the patterns of perchlorate deposition obtained in the study by Vella et al. which investigated the patterns of perchlorate dust deposition in different localities.[4] Vella et al. revealed that localities in the southern area of Malta had an overall higher concentration of perchlorate in dust fall when compared to the localities in the northern region, and overall higher levels in summer with persistence in lower concentrations during the other seasons. Resuspension of settled dust by the prevailing north-western wind which affects the island and higher use of fireworks in the summer were theories used to explain these variations.[4] On the other hand, the current study showed that the suburban areas in the Western and Northern regions, rather than the Southern regions, had higher incidences of hypothyroidism (Figures 3 and 4).

The high age-standardised rates obtained in the Western and Northern regions could relate to a higher number of farming communities in the area where locals tend to consume more of their own locally grown produce, which is potentially contaminated with perchlorate. Further research on consumption patterns in such localities can further help investigate any links with perchlorate exposure, especially as the majority of the Maltese population tend to consume imported food, which accounts for over 75% of total food consumption in the country.[11] These results were however not replicated in the island of Gozo where farming is more widespread than in Malta and could point towards a difference in the scale of firework fallout or indeed of packaging used – the other potential source of perchlorate.

There is no clear explanation for the statistically significant lower levels of hypothyroidism in some localities. However, Pembroke, Swieqi and San Gwann are three adjacent localities in the Northern Harbour District which are probably supplied with potable water solely from desalinated sea water from the Pembroke desalination plant. This is in contrast to other localities that are sourced with a mixture of groundwater and desalinated sea water depending on their geographical location. Since perchlorate levels tend to be much lower in sea water than in groundwater, perchlorate contamination of potable water from groundwater sources might be providing a small yet significant additional exposure to persons living in areas where potable water is sourced both from groundwater as well as seawater. This warrants further research into the levels of perchlorate in potable water by locality and by region.

LIMITATIONS

Some assumptions emanating from the ecological nature of this study were made when carrying out the data analysis, especially as the anonymised thyroid data set could not be enriched by linkages to other databases. For example, information on persons on treatment for thyroid disease was not available, and therefore, known hypothyroid cases with inadequate treatment may have been classified as a "new case" due to elevated TSH. Another assumption was made regarding the locality of residence, which was assumed to be the same as the locality registered in the central database of Malta. This is not always accurate as people may change address without updating the register. In addition, even if the locality of residence is correct, people may not spend most of their time there due to work, leisure, or other commitments. The study findings should thus be interpreted with caution.

The representativeness of the laboratory data used for the study may be affected by selection bias, especially as the data was not collected specifically for the aims of this study and did not follow strict screening criteria. This could have resulted in higher rates of detected hypothyroidism in those areas having better access to testing, especially when considering that mild hypothyroidism may not always give symptoms. However, given the access of private doctors to carry out testing for hypothyroidism in the public sector, this bias is expected to be small.

SUMMARY BOX

What is already known about the subject:

- The incidence of hypothyroidism is higher in women and in older age.
- Perchlorate exposure is one of the lesser-known causes of hypothyroidism.
- Health can be affected by exposure to various environmental contaminants.

What are the new findings

- Reported hypothyroid incidence varies geographically across the Maltese Islands.
- Potential reasons for this variation may include differences in dietary iodine intake and differential environmental exposures, such as perchlorate.
- This paper outlines areas for further potential research to study the effect of varying perchlorate exposure and health effects, and to study potential causes for the varying levels of hypothyroidism across the Maltese islands.

CONCLUSION

This study is the first to provide crude and age-standardised reported incidence rates for clinical and sub-clinical hypothyroidism in the Maltese islands by gender and locality. Despite the lack of clear patterns linking the incidence of clinical and sub-clinical hypothyroidism with perchlorate exposure, further monitoring is still warranted to expose the full extent of exposure to this compound. The fact that the Gozitan population has lower rates of hypothyroidism is a potential indication that people living in Malta are more exposed to potential environmental factors, including a more deficient iodine intake or higher perchlorate exposure, that are known to be linked to clinical or sub-clinical hypothyroidism. Finally, a study investigating the levels of perchlorate in potable water by region might provide further information on the clustering of high or low hypothyroidism rates in adjacent localities, which might be related to the potable water distribution system and the different sources of water in this network.

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