diseases and OLP or between thyroxin drug use and OLL, presumptively high because of the endemic status of thyroid diseases in our population and the consequent use of thyroxine-based drugs.

In conclusion, with regard to the findings by Siponen et al.,1 we do not think that the data to date show definitively an association between OLP/OLL and, at least, hypothyroidism, especially with the potential for biases from sample size calculation and consequently from type I error.

**REFERENCES**


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**Association of oral lichen planus with thyroid disease in a Finnish population: A retrospective case control study: “A different finding from a Mediterranean area”**

*In reply:*

We thank Dr Compilato et al. for their interest in our study and for sharing their own findings. We also fully agree with their statement “...we do not think the data to date show definitively an association between OLP/OLL and, at least, hypothyroidism” up to this point. Nothing in our article indicates a different conclusion; yet, we are unable to follow their argument to the end. For example, the meaning of “bias from sample size calculation” remains obscure to us, such a bias not being described in any well-known textbook on epidemiologic methods. Therefore, we would like to elaborate some methodological issues that we consider essential when evaluating observational evidence provided either by any single study, including theirs and ours, or jointly by several independent studies on the same question.

A major problem encountered in any epidemiologic study addressing the existence, direction, and strength of a conceivable association between thyroid diseases...
and OLP/OLL is the rarity of both conditions. This is particularly well demonstrated in the data of Dr Complilato et al. Presuming that the prevalence of OLP/OLL in a general population is only 1% to 3%, it is not much less from what one would expect that only 1 case of OLP was found in their small cohort comprising 74 patients with Hashimoto’s thyroiditis or Graves disease, and no cases in the even smaller comparison group of 51 goiter patients. The crude odds ratio computed from these figures, taken at their face value, has a point estimate of (1/73)/(0/51), which equals plus infinity. Moreover, the 95% confidence interval (computed by the exact method based on the noncentral hypergeometric distribution), would extend from .02 to plus infinity!

The range of uncertainty as reflected by the above result is naturally in full accordance with the null hypothesis of no association (odds ratio [OR] = 1). Yet, the enormous width of this error margin implies a very good agreement with our findings (point estimate OR ~ 2), too, but also with such a possibility—quite implausible a priori, though—that the true relative risk of OLP/OLL in patients with thyroid disease could even have a much higher value than the highest upper confidence limit (OR ~ 6) reported in our article. Therefore, unfortunately, the empirical data of Compilato et al. actually contains extremely little evidence on the possible association between thyroid disease and OLP/OLL.

Compared with the cohort design as applied by Compilato et al., our case-control design was statistically clearly more efficient. Of our 222 cases of OLP/OLL and 222 healthy controls, the subset that essentially determines the amount of statistical information comprised 21 exposed cases and 11 exposed controls. This is in a striking contrast with the information provided by the numbers of exposed (1) and unexposed (0) cases, respectively, of Compilato et al. As a consequence, the confidence intervals of all the OR estimates computed in our article were so much narrower. To obtain a similar precision (or “power”) as we had, the size of a cohort of patients with thyroiditis would need to be at least 500 in case the true prevalence of OLP/OLL were 3%. If this prevalence were only 1%, then the necessary cohort size would be more than 1500. In both instances, the size of the comparison cohort would have to be at least as large as the thyroiditis cohort.

Epidemiologic evidence contained in any single observational study, ours included, must always be interpreted with due caution because of the possibility of (1) residual confounding caused by unknown factors, (2) selection bias, and (3) information bias, the latter owing to incompleteness in measurements and classifications. Taking into account these possibilities, as well as the remaining statistical imprecision in our own estimates, we do admit that the evidence provided by our study only is relatively weak. However, when interpreting our result we already noted in our article that it is essentially replicating the findings of the same direction in 2 previous studies from Denmark and Israel, thus strengthening the evidence base on the association of interest. In any informal synthesis of evidence or a more formal meta-analysis based on independent studies, the possibility of “Type I error” in any single study is relevant only if there is substantial publication bias favoring so-called “positive” result. Also, even if a large number of studies contained a “nonsignificant” result, they would not as such represent evidence that would be seriously conflicting with the “positive” findings, as long as all these “negative” results were coupled with wide confidence intervals about the null hypothesis value—as quite often is the case.

Nevertheless, the evidence base on the association between thyroiditis/thyroid diseases and OLP/OLL is still inadequate for definite conclusions. Therefore, with all the above considerations already implicitly in mind, we closed the discussion section in our article: “Other studies with larger sample sizes from different parts of the world are needed to add further evidence for this association.” We would be very happy to see such studies from Italy, too.

Esa Läärä
Department of Mathematical Sciences
Faculty of Science
University of Oulu
Oulu, Finland

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