Response to Grimes and Newton et al.

Peckham S, Lowery D and Spencer S

Grimes and Newton et al. have made a number of criticisms of our paper, including: that we misrepresent conclusions of the existing literature; do not adequately take account of confounding factors; have used arbitrary cut-offs in categorising the variables; and made an error in reporting the results of the model.[1,2] We welcome the opportunity to respond to these criticisms and, in particular address the claim made by Newton et al that we made an error in reporting the results of our model. We acknowledge the substantial problem of poor oral health that affects some children and adults in the UK and do not question that there is substantial good quality evidence to support the topical use of fluorides in toothpaste, nor do we wish to see the removal of effective and safe oral health programmes. The paper is not a discussion of the benefits or otherwise of water fluoridation programmes as these are discussed elsewhere.[3,4,5] The focus of our paper was on whether fluoride levels in drinking water were associated with the prevalence of hypothyroidism.

Journal restrictions on paper length and number of references meant that we were not able to fully discuss the literature on fluoride and the thyroid. Consequently, we referred to the discussion from the NRC report, believing that to provide a sufficient basis to consider a plausible relationship.[6] We accept that the primary causes of hypothyroidism are varied, including autoimmune disease and surgical intervention. Grimes states that the NRC report does not support a link between water fluoridation and thyroid function.[1] However, the NRC authors did identify an association between fluoride intake and thyroid function concluding that: "*In humans, effects on thyroid function were associated with fluoride exposures of 0.05-0.13 mg/kg/day when iodine intake was adequate and 0.01-0.03 mg/kg/day when iodine intake was inadequate* (Table 8-2)." (p263).[6]

In undertaking our analysis we adjusted for age and sex as the two major confounding issues; and also reviewed whether there was any evidence to show a clear geographical variation in perchlorate exposure and iodine intake. We only found one analysis of perchlorate levels, which suggested this probably was not an important confounder in the UK.[7] Iodine intake is clearly more critical in terms of thyroid function. Both Grimes and Newton et al reference the same paper by Vanderpump et al we included in our paper to support their claim that iodine intake variation may be the reason for differing hypothyroid levels observed in our paper.[8] However, this study only included school aged girls in nine schools across the UK. Individual and practice level iodine status data is unavailable; consequently, we reviewed whether there was evidence of significant iodine intake variation by geographical area utilising the National Geographic Survey data (BGS) and the National Diet and Nutrition Surveys (NDNS).[9,10] The British Geological Survey concluded that generally all topsoil (except for some coastal areas) is iodine deficient; but given that soil and water iodine content contributes such a small part of total iodine intake, these differences across the UK are unlikely to affect total iodine intake. It is estimated that average daily iodine intake comprises 156 ug/L per day from food (42% from dairy produce), 12 ug/L from air and 12 ug/L from water. The NDNS shows that for women over the age of 40 years, iodine intake is above the recommended daily intake in all regions of the UK (see figures 1s and 2s). Thus it seemed reasonable to conclude that iodine intake was not a sufficient reason for the variation observed in our analysis.

Our rationale for comparing two urban areas was to compare a fluoridated and non-fluoridated area with similar socio-demographic characteristics. The West Midlands is the only wholly fluoridated area; and non-fluoridated comparator areas are limited. Comparisons between the West Midlands and Manchester are often used in studies examining fluoridation and dental caries. Consequently, it seemed reasonable to use these areas for this comparison as well.

Originally we intended to present an analysis utilising more statistically powerful linear regression modelling. However, on submission we were asked by the journal referees to present the data as odds ratios in a binary form. The main advantage would be that treating data categorically is more closely aligned with a 'clinical' approach; consequently, results can be more meaningfully interpreted by the journal readership. We agreed to this recommendation because it seemed to have a nominal impact on the results.

The unpublished linear regression model accounted for 51% of the variance. We include here a table with the unstandardised β coefficients from that model (Table 1s); which predicts that practice level hypothyroidism prevalence will be 0.03% higher for each additional 0.1mg/L of maximum fluoride. In other words, it predicts that an average sized practice (7022 patients) located in an area maximally fluoridated to 1mg/L will have an additional seventeen cases of hypothyroidism, in comparison to a similar size practice located in an area fluoridated up to 0.2 mg/L.

For the published binary model, we selected the level of <0.3mg/L as it is considered that below this level there are no dental health effects. The higher threshold (0.7mg/L) was chosen because most countries that fluoridate (e.g. Canada, Ireland, USA) give 0.7mg/L as the lower limit of the target range for artificially fluoridating drinking water supplies.

A key criticism made by Newton et al is that we have made a basic error in our analysis. We have re-checked our analysis and can confirm that all the results we reported in our original paper are correct. However, we concur with Newton et al that the unadjusted odds of a practice recording 'high' hypothyroidism prevalence is less if it is in an area from the upper two tertiles of IMD (OR 0.49; 95% CI: 0.44, 0.54). We carried out some exploratory analysis and found that the direction of prediction switches when adjusting for the 'proportion of people over 40 registered with practice'. This may be an inconsistent mediating or confounding effect. In our published paper we did not report unadjusted odds ratios for all the variables included in the model. Perhaps we could have made this clearer, and so we provide the unadjusted and the adjusted odds ratio for each of the variables included in the final logistic regression model here (Tables 2s & 3s). We hope this is informative. Incidentally, removing IMD nominally degrades the unpublished linear regression model.

We accept that association is not causation; but clearly our findings suggest an important association within a large population. Despite the recognised problems of this type of study, we believe our paper raises important questions that deserve further attention. As Sutton et al acknowledge the "… *study suggests that fluoride in water may be linked to the development of hypothyroidism, but observational epidemiological studies (such as cohort and case-control study designs) are required in order to prove causality.*"[11] (84)

References:

1. Grimes DR. Commentary on "Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water". *Journal of epidemiology and community health*. 2015 Mar 18:jech-2015

2. Newton JN, Young N, Verne J, Morris J. Water fluoridation and hypothyroidism: results of this study need much more cautious interpretation. *Journal of epidemiology and community health*. 2015 Jul 1;69(7):617-8.

3. Iheozor-Ejiofor Z, O'Malley LA, Glenny AM, Macey R, Alam R, Tugwell P, Walsh T, Welch V, Worthington HV. *Water fluoridation for the prevention of dental caries.* The Cochrane Library. 2015.

4. McDonagh, S. Marian, P. F.Whiting et al., *A Systematic Review of Public Water Fluoridation*, NHS Centres for Reviews and Dissemination Report 18, 2000; University of York, York, UK.
5. Warren JJ, Levy SM, Broffitt B, Cavanaugh JE, Kanellis MJ, and Weber-Gasparoni K, "Considerations on optimal fluoride intake using dental fluorosis and dental caries outcomes— a longitudinal study," *Journal of Public Health Dentistry*, vol. 69, no. 2, pp. 111–115, 2009.

6. National Research Council (NRC*). Fluoride in drinking water: a scientific review of EPA's standards*. Washington DC: National Academies Press, 2006.

7. Blake S, Hall T, Harman M, Kanda R, McLaughlin C, Rumsby P. *Perchlorate – risks to UK drinking water sources.* DEFRA 7845 (DWI70/2/218) Swindon 2009.

8. Vanderpump M, Lazarus J, Smyth P, et al. Iodine status of UK schoolgirls: a cross-sectional survey. *Lancet* 2011;377:2007–12.

9. BGS Commissioned report CR/03/057N - http://www.bgs.ac.uk/research/international/DFID-KAR/CR03057N_COL.pdf)

10. National Diet and Nutrition Survey *Headline results from Years 1 and 2 (combined) of the rolling programme 2008-9 - 2009-10* http://webarchive.nationalarchives.gov.uk/20130402145952/https://www.gov.uk/government/publications/national-diet-and-nutrition-survey-headline-results-from-years-1-and-2-combined-of-the-rolling-programme-2008-9-2009-10.

11. Sutton M, Kiersey R, Farragher L, Long J. *Health effects of water fluoridation*. 2015. Health Research Board, Ireland.

Table 1s: Adjusted unstandardized β coefficients according to each of the variables included in the final published model utilising multiple linear regression modelling.

	Unstandardised β	(95% CI)
Proportion of Females registered with Practice (%)	0.058	0.051-0.065
Proportion of people over 40 registered with Practice (%)	0.071	0.069-0.073
Index of Multiple Deprivation	0.003	0.002-0.005
Maximum fluoride (mg/L)	0.333	0.282-0.383

Table 2s: Unadjusted Odds Ratio of upper tertile hypothyroidism prevalence according to each of the variables included in the final model.

	OR	Fluoride level 95% CI
Proportion of Females registered with Practice (%)	1.24	1.21 - 1.27
Proportion of people over 40 registered with Practice (%)	1.18	1.17 - 1.19
Index of Multiple Deprivation 'Medium'	0.76	0.68 - 0.85
Index of Multiple Deprivation 'High'	0.28	0.25 - 0.32

Table 3s Adjusted odds ratios of upper tertile hypothyroidism prevalence according to fluoride levels in drinking water, adjusted for proportion of females registered with the practice and proportion of patients over 40 years old registered with the practice.

	OR	Fluoride level 95% CI
Maximum fluoride >0.7 mg/L	1.68	1.43 - 1.98
Maximum fluoride >0.3 ≤ 0.7 mg/L	1.34	1.09 - 1.63