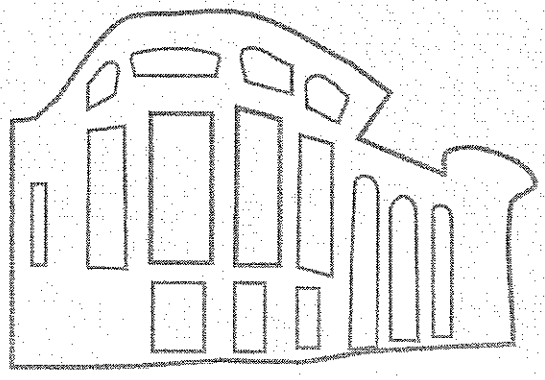
Proceedings of

COMPSTAT 2016

22nd International Conference on Computational Statistics



August 23-26, 2016

Auditorio Príncipe Felipe, Oviedo, Spain

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22nd International Conference on Computational Statistics

COMPSTAT 2016

23-26 August 2016
Oviedo, Spain

Editors:
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Technical Editors:
Gil Gonzalez-Rodriguez and Angela Blanco.

ISBN/EAN: 978-90-73592-36-0
1st August 2016

Preface

The 22nd International Conference on Computational Statistics, COMPSTAT 2016, is held in Oviedo, Spain, from August 23rd to August 26th 2016. It is locally organized by members of the University of Oviedo assisted by active Spanish researchers. The COMPSTAT is an initiative of the European Regional Section of the International Association for Statistical Computing (IASC-ERS), a society of the International Statistical Institute (ISI). COMPSTAT is one of the best-known world conferences in Computational Statistics, regularly attracting hundreds of researchers and practitioners.

The first COMPSTAT conference took place in Vienna in 1974, and the last two editions took place in Limassol in 2012 and Geneve in 2014. It has gained a reputation as an ideal forum for presenting top quality theoretical and applied work, promoting interdisciplinary research and establishing contacts amongst researchers with common interests.

Keynote lectures are addressed by Prof. Gerard Biau, Universit Pierre et Marie Curie, Paris, France, Prof. Alastair Young, Imperial College, London, UK and Prof. Hans-Georg Mueller, University of California Davis, United States.

From more than 450 submissions received for COMPSTAT, 360 have been retained for presentation in the conference. The conference programme has 41 contributed sessions, 8 invited sessions, 3 keynote talks, 30 organized sessions and 3 tutorials. There are approximately 430 participants.

The Proceedings are published in an electronic book comprising 34 papers. The participants can find an electronic copy in a USB stick placed in their conference bags or download it at the conference web page. All the papers submitted have been evaluated through a rigorous peer review process. Those papers that have been accepted for publication in the Proceedings have been evaluated thoroughly by at least 2 referees. This ensures a high quality proceedings volume in the main areas of computational statistics.

The organization would like to thank the editors, authors, referees and all participants of COMPSTAT 2016 who contributed to the success of the conference. Our gratitude to sponsors, scientific programme committee, session organizers, local universities, the city of Oviedo, and many volunteers who have contributed substantially to the conference. We acknowledge their work and support.

The COMPSTAT 2016 organizers invite you to the next edition of the COMPSTAT, which will take place in Iasi, Romania in 2018. We wish the best success to Cristian Gatu the Chairman of the 23rd edition of COMPSTAT.

Ana Colubi
Organiser and Chairperson of the SPC.

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Contents

NPC to assess effects of maternal iodine nutrition and thyroid status on children cognitive development

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Abstract. Maternal iodine nutrition and thyroid status may influence neurocognitive development in children. This study investigated the effects on the intelligence quotient (IQ) of children born to mothers with different levels of iodine supplementation, with or without the administration of levothyroxine (LT4), prior to and during pregnancy. From a methodological point of view, we used the Non Parametric Combination test or NPC test, based on permutation solution. It was chosen for the several optimal properties of which it is characterized, that make it very flexible and widely applicable in many fields; in particular, it allows stratified analyses and represents an effective solution for problems concerning the testing of multidimensional hypotheses, that are difficult to face in a parametric context.

Keywords. NPC test, Neurocognitive Development, Iodine Nutrition, Thyroid Status.

1 Introduction

Thyroid hormone (TH) is required for normal brain development. Prior to the onset of fetal thyroid function, the mother is the only source of TH for the developing brain. By 16-20 weeks post-conception the fetal thyroid is mature enough, and from this point in time onwards the fetus cooperate to make up his own TH pool [34]. However, the relative contribution of the mother and the fetus to the regulation of TH-dependent processes within the brain is not yet fully established.

Since iodine is essential for TH synthesis [24], a gestational intake of this micronutrient that fails to meet the needs of pregnancy may simultaneously impair both maternal and fetal TH production [15]. Accordingly, the most serious consequence of gestational iodine deficiency (ID) is endemic cretinism, due to severely impaired TH synthesis in the mother and fetus from early pregnancy onwards [15]. In conditions of mild to moderate ID, less severe degrees of maternal thyroid insufficiency may occur over gestation [19], [22], and several studies have shown these conditions to be associated to minor neuropsychiatric and intellectual deficits in progeny [27], [15], [33], [20] and [23]. On the other hand, other studies carried out in iodine sufficient regions failed to confirm these associations, with some reports anecdotally reporting normal neurodevelopment in children born to mothers who were severely hypothyroid for causes other than ID [18] and [26]. Finally, a growing body of evidence has recently been provided, overall indicating

that gestational iodine supplementation, while not having a clear impact on maternal thyroid function [35], [21] is actually effective in improving infant cognitive development [6]. By contrast, iodine supplementation given in later stages of life, i.e. during adulthood, while improving iodine status, proved to have no impact on cognitive function [31]. Since potential mechanisms by which iodine affects cognition include white matter maturation, the observed lack of effect of iodine supplementation on the cognitive scores of mildly iodine-deficient young adults has been attributed to the fact that the process of myelination is more complete in adulthood compared to fetal life and infancy, and therefore less malleable [31].

Taken as a whole, these data might be consistent with the hypothesis that maternal iodine status primarily influences fetal thyroid function, which may play a more critical role than maternal thyroid function in determining neuro-intellectual outcomes in progeny. In order to assess this assumption, a prospective study was carried out on schoolchildren living in an ID area and born to mothers exposed to different iodine supplementation regimens, half of whom had been receiving levo-thyroxine (LT4) prior to and during pregnancy in order to guarantee maternal euthyroidism throughout gestation [25]. The main results of this study were that children born to mothers with similar iodine intake during pregnancy had comparable intellectual abilities, regardless of their mothers' thyroid function. Conversely, children born to mothers with comparable thyroid function during pregnancy, namely those born to mothers on LT4 therapy, performed differently on intelligence quotient (IQ) tests, with those born to mothers who had been receiving iodine supplementation during pregnancy showing significantly higher IQ scores than those born to unsupplemented mothers. Indeed, logistic regression models designed to assess the dependence of suboptimum cognitive outcomes (IQ<85 points) on various explanatory variables failed to show a significant association with maternal thyroid parameters at any stage in pregnancy, whereas maternal iodine status proved to be positively associated with cognitive outcomes.

In this study we aimed at evaluating the intelligence quotient (IQ) of children born to mothers with different levels of iodine supplementation, with or without the administration of levothyroxine (LT4), prior to and during pregnancy. In particular we focused our attention on some mother-child pairs and we compared them according to iodized salt consumption and LT4 treatment.

2 The Data

The examined sample included four groups, each comprising 25 mother-child pairs, identified on the basis of maternal histories of iodized salt consumption and LT4 treatment prior to and during pregnancy. The groups were labeled as follows: iodine (I), no iodine (no-I), iodine + LT4 (I+T4) and no iodine + LT4 (no-I+T4). Inclusion criteria for the mothers were:

a) age>18 years;
b) singleton and uncomplicated pregnancy;
c) term delivery;
d) no severe or chronic diseases (including thyroid autoimmune diseases);
e) no major post-partum complications (including post-partum depression);
f) thyroid function evaluation throughout gestation;
g) full diet and lifestyle information during pregnancy and afterwards;
h) informed consent.

Inclusion criteria for the children were:

a) age between 6 and 14 years;
b) no major neonatal complications (including birth trauma);
c) no congenital hypothyroidism;
d) no severe or chronic diseases;
e) no ascertained major cognitive deficits;
f) regular education;
g) approval to cognitive test administration.

Child Intelligence Quotients (IQ) was assessed with the use of Wechsler Intelligence Scale for Children - Third Edition (WISC-III), which was administered by trained psychologists who were blinded as to which group subjects were allocated. The Full-Scale IQ (FSIQ), the Verbal IQ (VIQ) and the Performance IQ (PIQ) were calculated for each child and used into analysis.

For each mother the following information was collected: Triiodothyronine (T3), Thyroxine (T4), Thyroid-stimulating hormone (TSH), Free Triiodothyronine (FT3) and Free Thyroxine (FT4) for assessing maternal thyroid status at each point in time during gestation (recorded in the following weeks range: 4-12, 13-18, 19-24, 25-30, 31-36), Urinary Iodine Concentrations (UIC), family Socio-Economic Status (S.E.S.) evaluated by means of Hollingshead Index, iodized salt consumption (yes or no) and L-T4 treatment (yes or no).

3 The Non Parametric Combination Test (NPC)

The non-normality in the distribution of the considered phenomena (as verified by Kolmogorov Smirnov test) does not guarantee valid asymptotic results; consequently the non-parametric approach has been used. In particular we used the Non Parametric Combination (NPC) test, based on permutation test [30], [10], chosen for the several optimal properties of which it is characterized. Permutation tests [29], [16] represent an effective solution for problems concerning the verifying of multidimensional hypotheses, because they are difficult to face in parametric context. This multivariate and multistrata procedure allows to reach effective solutions concerning problems of multidimensional hypotheses verifying within the non parametric permutation inference [28]; it is used in different application fields that concern verifying of multidimensional hypotheses with a complexity that can not be managed in parametric context. In comparison to the classical approach, NPC test is characterized by several advantages:

- it doesn't request normality and homoscedasticity assumption;
- it draws any type of variable;
- it also assumes a good behavior in presence of missing data;
- it is also powerful in low sampling size;
- it resolves multidimensional problems, without the necessity to specify the structure of dependence among variables;
- it allows to test multivariate restricted alternative hypothesis (allowing the verifying of the directionality for a specific alternative hypothesis);
- it allows stratified analysis;
- it can be applied also when the sampling number is smaller than the number of variables.

All these properties make NPC test very flexible and widely applicable in several fields; in particular we cite applications in sociological context [5], [3], [7], in medical context [37],[4], [1], [8], [36], [2], [32], [9] and in genetics [13], [12].

We supposed to notice K variables on N observations (dataset N×K) and that an appropriate K-dimensional distribution P exists. The null hypothesis postulates the equality in distribution of k-dimensional distribution among all C groups

$$H_0 = [P_1 = ... = P_C] = [X_1 \stackrel{d}{=} ... \stackrel{d}{=} X_C]$$
$$\text{i.e. } H_0 = \cap_{i=1}^{k} X_{1i} \stackrel{d}{=} ... \stackrel{d}{=} X_{Ci}] = [\cap_{i=1}^{k} H_{0i}]$$

against the alternative hypothesis

$$H_1 = \cup_{i=1}^{k} H_{1i}.$$

Let's assume that, without loss of generality, the partial tests assume real values and they are marginally correct, consistent and significant for great values; the NPC procedure (based on Conditional Monte Carlo resampling) develops into the following phases, such as illustrated in Figure 1.

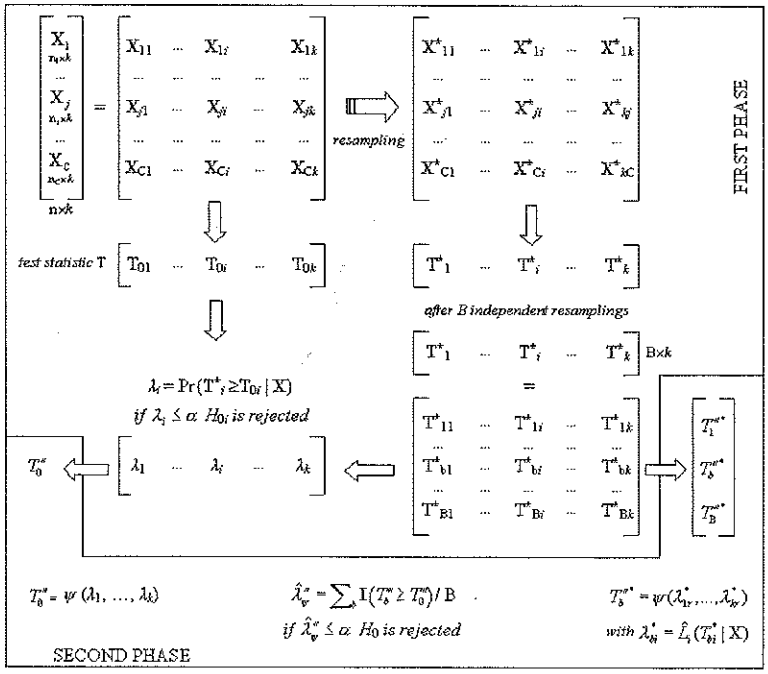

Figure 1. Two-phases NPC algorithm

The null hypothesis, that postulates the indifference among the distributions, and the alternative one are expressed as follows:

$$H_0 : \left\{ X_{11} \stackrel{d}{=} X_{12} \right\} \cap \cdots \cap \left\{ X_{n1} \stackrel{d}{=} X_{n2} \right\} \tag{1}$$

$$H_1 : \left\{ X_{11} \stackrel{d}{\neq} X_{12} \right\} \cup \cdots \cup \left\{ X_{n1} \stackrel{d}{\neq} X_{n2} \right\} \tag{2}$$

In presence of a stratification variable, the hypotheses system is:

$$H_{0i} : \left\{ X_{11i} \stackrel{d}{=} X_{12i} \right\} \cap \cdots \cap \left\{ X_{n1i} \stackrel{d}{=} X_{n2i} \right\} \tag{3}$$

$$H_{1i} : \left\{ X_{11i} \stackrel{d}{\neq} X_{12i} \right\} \cup \cdots \cup \left\{ X_{n1i} \stackrel{d}{\neq} X_{n2i} \right\} \tag{4}$$

The hypotheses systems are verified by the determination of partial tests (first order) that allow to evaluate the existence of statistically significant differences. By means of this methodology we can preliminarily define a set of k (k>1) unidimensional permutation tests (partial tests); they allow to examine every marginal contribution of answer variable, in the comparison among the examined groups. The partial tests are combined, in a non parametric way, in a second order test that globally verifies the existence of differences among the multivariate distributions. A procedure of conditioned resampling CMC (Conditional Monte Carlo) allows to estimate the p-values, associated both to partial tests and to second order tests.

Under the exchangeability data among groups condition, according to null hypothesis, NPC test is characterized by two properties:

- similarity: whatever the underlying distribution data, the probability to refute the null hypothesis is invariant to the actually observed dataset, whatever the type of data collection;
- for each α, for each distribution and for each set of observed data, if under the alternative hypothesis, the distribution dominates the null hypothesis, then an unbiased conditional test exists and, therefore, the probability of refuting the null hypothesis is always no less than the α significance level.

4 The results

The analysis was performed comparing four groups, defined on the basis of maternal histories of iodized salt consumption and LT4 treatment prior to and during pregnancy:

- Group A= iodine (I);
- Group B= iodine + LT4 (I + T4);
- Group C= no iodine and no LT4 (no-I);
- Group D= no iodine + LT4 (no-I + T4).

In Table 1 we report the results of the NPC test; all combined p-values are obtained using Fisher's combining function.

Table 1. Mean values and p-values for groups comparison

VARIABLES	**Group A**	**Group B**	**Group C**	**Group D**	**p-value**
Week birth	38.40	38.36	38.73	38.33	0.780
Weight birth	3241.1	3164.2	3171.4	3292.2	0.646
FSIQ	93.13	96.07	81.73	81.27	**0.012**
VIQ	90.07	97.29	80.33	79.60	**0.006**
PIQ	98.20	96.43	87.33	87.53	0.111
Child age	9.247	9.825	10.52	10.20	0.390
Mother age	29.53	29.07	27.67	28.87	0.622
UIC	90.07	124.7	51.27	73.87	**0.001**
S.E.S.	18.53	19.82	16.83	21.67	0.374
T3(4-12)	171.7	156.6	168.9	147.5	0.332
T4 (4-12)	11.92	12.60	12.19	11.95	0.913
FT3 (4-12)	3.791	4.180	3.856	3.585	0.072
FT4 (4-12)	17.96	19.15	14.74	17.69	**0.002**
TSH (4-12)	0.613	0.526	0.828	0.722	0.254
T3(13-18)	185.3	178.9	186.7	168.7	0.690
T4 (13-18)	12.39	12.66	11.70	12.45	0.726
FT3 (13-18)	3.932	4.426	3.866	3.783	0.093
FT4 (13-18)	16.42	17.40	12.53	15.80	**0.000**
TSH (13-18)	0.776	0.556	1.193	0.829	**0.009**
T3(19-24)	193.7	188.5	181.1	168.9	0.447
T4 (19-24)	11.69	13.91	11.81	13.49	0.062
FT3 (19-24)	4.063	3.913	3.659	3.860	0.334
FT4 (19-24)	14.72	16.40	12.64	16.63	**0.000**
TSH (19-24)	0.982	0.495	1.225	0.583	**0.000**
T3(25-30)	188.1	191.8	184.7	181.4	0.931
T4 (25-30)	11.67	12.95	12.04	13.81	0.094
FT3 (25-30)	3.824	3.986	3.620	3.645	0.362
FT4 (25-30)	14.10	15.80	12.28	16.47	**0.000**
TSH (25-30)	0.995	0.449	1.302	0.376	**0.000**
T3(31-36)	178.3	188.1	174.9	172.6	0.651
T4 (31-36)	11.88	14.05	11.94	13.06	0.059
FT3 (31-36)	3.620	3.819	3.579	3.505	0.594
FT4 (31-36)	13.77	16.62	12.22	16.41	**0.000**
TSH (31-36)	0.959	0.355	1.454	0.330	**0.000**
					↓
Combined					**0.000**

As we can see, significant differences exists among the four analyzed groups, with reference to FSIQ, VIQ, maternal UIC and the serum of TSH and TF4 in different times of observation. So, for only these variables, we performed the two-by-two comparison between groups. For these multiple comparisons, we had to apply Bonferroni's correction; the number of possible comparisons that can performed with four groups are 6, so the adjusted significance level for this analysis was equal to $\frac{0.050}{6} = 0.008$.

Table 2. Partial and Combined p-value for two-by-two comparisons

VARIABLES	**A vs B**	**A vs C**	**A vs D**	**B vs C**	**B vs D**	**C vs D**
FSIQ	0.603	0.022	0.014	0.026	0.017	0.942
VIQ	0.250	0.058	0.048	**0.007**	**0.006**	0.895
UIC	**0.001**	**0.000**	0.074	**0.000**	**0.000**	0.026
FT4 (4-12)	0.515	**0.000**	0.763	**0.001**	0.419	**0.002**
FT4 (13-18)	0.401	**0.000**	0.566	**0.001**	0.267	**0.003**
TSH (13-18)	0.182	0.012	0.790	**0.002**	0.199	0.078
FT4 (19-24)	**0.006**	**0.004**	0.018	**0.000**	0.812	**0.000**
TSH (19-24)	0.010	0.314	0.016	**0.002**	0.538	**0.001**
FT4 (25-30)	**0.007**	0.013	**0.005**	**0.000**	0.452	**0.000**
TSH (25-30)	**0.005**	0.211	**0.001**	**0.000**	0.558	**0.000**
FT4 (31-36)	**0.000**	0.045	**0.006**	**0.000**	0.832	**0.001**
TSH (31-36)	**0.001**	0.020	**0.000**	**0.001**	0.821	**0.000**
	↓	↓	↓	↓	↓	↓
Combined	**0.000**	**0.000**	**0.000**	**0.000**	**0.002**	**0.001**

The result highlight that offspring of mothers belonging to groups A (Iodine) and B (iodine + LT4) had similar Verbal, Performance and Full-Scale Intelligence Quotients; all these IQ were higher than children born to no-I and no-I + T4 mothers (groups C and D, respectively). Moreover, a further analysis was also performed aggregating Groups A and B (iodine) and Groups C and D (No-iodine) in order to evaluate effects of maternal iodine nutrition.

Table 3. Mean values and p-values for comparison between Iodio vs No-Iodio groups

VARIABLES	**Iodine**	**No-Iodine**	**p-value**
FSIQ	94.55	81.50	**0.001**
VIQ	93.55	79.97	**0.001**
UIC	106.8	62.57	**0.000**
FT4 (4-12)	18.53	16.22	**0.005**
FT4 (13-18)	16.89	14.16	**0.001**
TSH (13-18)	0.670	1.011	**0.013**
FT4 (19-24)	15.53	14.64	0.209
TSH (19-24)	0.747	0.904	0.315
FT4 (25-30)	14.92	14.38	0.438
TSH (25-30)	0.731	0.839	0.516
FT4 (31-36)	15.15	14.31	0.284
TSH (31-36)	0.667	0.892	0.188
			↓
Combined			**0.001**

Defective cognitive function (in term of FSIQ and VIQ) was significantly higher in the children of mothers not using iodized salt than of those mothers using it. Also UIC results to be significantly higher in mothers who use iodized salt. The use of iodized salt also implies a significant increase in FT4 values in the period between 4 and 18 weeks of pregnancy.

We underline also that the TSH values are significantly reduced in the weeks 13-18 for the only women who consume iodized salt. The other examined variables show no significant difference between the two compared groups.

5 Final remarks

Thyroid hormone is essential for normal pregnancy progression and brain development. Impairments in maternal thyroid function are associated to several obstetrical complications [17],[11]. They require prompt intervention, bearing in mind that both maternal thyroid disease per se and related treatments may adversely affect the newborn's health [17] and [14].

From a methodological point of view, in this paper we aim to show as the permutation tests are very helpful in medical contexts, in particular in the endocrinological research. We applied permutation tests to perform comparison between four groups of children, defined on the basis of maternal histories of iodized salt consumption and LT4 treatment. Examining the results achieved by applying NPC tests, we have to notice an interesting result: defective cognitive function (in term of FSIQ and VIQ) was significantly higher in the children of mothers not using iodized salt, than of those mothers using it. Also UIC results to be significantly higher in mothers who use iodized salt.

So, our research emphasizes the importance of taking iodine in pregnancy to the child's future welfare. It also shows how much a lack of iodine may hinder children into reaching their full intellectual potential. An inadequate maternal iodine intake during pregnancy may result in cognitive impairment in later life, likely because of an insufficient fetal TH output due to reduced iodine storage in the fetal gland. Therefore, based on the obtained results, we can affirm that children, whose mothers took the right amount of iodine during pregnancy, exhibit more learning and cognitive abilities and are more intelligent than children whose fetal life was marked by a low iodine intake.

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