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Analysis of Impact of Salt Consumption by Applying Meta-Analysis Statistical Techniques

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Abstract

Many fatal diseases can be avoided by controlling unhealthy diet that includes high proportion of salt-intake in everyday usage. Salt intake and its impact on various health parameters (blood pressure, hypertension, cardiovascular) are well documented in literature. New data on salt-intake impacts is being generated at a very rapid rate. In order to comprehend the full scope of the dietary control and its impact on controlling related diseases, a rigorous statistical analysis is required. Meta-analysis has emerged as a powerful tool for synthesizing complex data coming from various studies. In this work, it was identified the need of developing MATLAB models that can be used to perform meta-analysis on the given data originating from various resources. For this purpose, two MATLAB models are developed. These MATLAB models perform meta-analysis synthesis on the data by using fixed effect model for both continuous and binary data. Both MATLAB models are validated against the example data provided in literature and were found accurate. As a preliminary step, the MATLAB program based on fixed effect model for continuous data was used to investigate salt-intake data from four independent studies. Preliminary results (size effect, weight assigned to each size, estimation of summary effect, Z value, 95% confidence interval, and P values) show that the model is robust and may be implemented on a larger scale.

Keywords: Salt-Intake, Meta-Analysis, MATLAB, Fixed Effect Models

1. Introduction

Cardiovascular diseases (CVDs) encompass a large range of heart and vessel disorders that are responsible for 31% of all deaths in 2016. Most CVDs can be avoided by addressing behavioral risk factors (unhealthy diet, obesity, and smoking). An unhealthy diet is one marked by overeating and consuming high amounts of salt, sugar, and/or fats. Various research groups have analyzed data associated with salt consumption and its impact on CVDs. To understand the research results of one study in the context of all other studies appears as the main concern. Statistical methods based on "Meta-Analysis" synthesizing data rather than taking individual research results are preferred[1]. In recent decades, meta-analysis has emerged as a powerful tool to analyze randomized, control trials data in an effective and meaningful manner. While many individual trials for the same medial application may use different analysis techniques and may not be able to reach on any consensus on the trials, meta-analysis will assist to draw some sort of conclusion on those studies. This can be seen in many research studies where meta-analysis was used to give a different

perspective to the problem under review. Lau et. al., for instance, were successful to apply meta-analysis techniques on therapeutic trial for myocardial infarction[2]. They performed cumulative meta -analysis of clinical trials that evaluated 15 treatments and preventive measures for acute myocardial infarction. Thirty-three trials evaluating this therapy performed between 1969 and 1988 were included in this study. Findings of this study clearly indicated that the meta-analysis technique successfully facilitated the determination of clinical efficacy and harm, and was helpful in tracking trials, planning future trials, and making recommendations for therapy[2]. Other noticeable work cited in references [3,4,5] has indicated successful use of meta-analysis of randomized control trials conducted by various groups around the globe.

One important area where meta-analysis approach is highly desirable is related to the impact of salt intake on obesity, hypertension, cardiovascular diseases, and strokes. Sarmugam et al. work reviewed the current levels of salt knowledge and its association with dietary salt intake and salt-related dietary practices in the general population[6]. Ma et al.[10] also looked at the impact of high salt intake and investigated associated risk factor for obesity. Their results suggested that salt intake is a potential risk factor for obesity independent of energy intake. A similar study was conducted by Alawwa et al.[7] where they estimated the average sodium intake in a sample of healthy adult diet and also assessed participants' knowledge, attitudes, and behavior towards dietary salt intake. Strazzullo et al.[8] also assessed the relation between the level of habitual salt intake and stroke or total cardiovascular disease outcome[3]. In their study 19 cohort samples from 13 studies, with 177025 participants and over 11000 vascular events were analyzed. This study found that high salt intake is associated with significantly increased risk of stroke and total cardiovascular disease[8].

As the clinical data on salt intake and its impacts is being generated at a rapid rate, an update on the data analysis is highly desirable. In this regard, first important step will be to develop robust model programs that can be provided as an open-ended tool for research in this field. In this work we develop two meta-analysis programs/models that were based on "Fixed Effect Model" and use MATLAB as the programing tool. These programs/models perform meta-analysis synthesis on the data by investigating different elements including "the size effect" of each study involved, "the weight" assigned to each effect size, and the estimation of the summary effect by keeping in view the significance intervals, precisions and p-values. One model starts with the mean, standard deviation, and sample size of the given data on various studies and then uses the bias-corrected standardized mean difference (Hedges' g) as the effect size measure. Second model starts with the events and non-events in two independent groups from different studies and used the odd ratio as the effect size measure. Both models have been validated against the test examples described by Borenstien et al[1]. In the second step, one of the models was used to analyze salt intake impact and for this purpose four studies conducted by Dyer et al[9], Ma et al.[10], Radhika et al.[11], and Yang et al[12] were selected for collecting data. Following sections describe in a greater detail both meta-analysis models and summarize the results (standard mean difference, 95% confidence interval, Z value, and the p-values for both one-tailed or two-tailed scenarios) for four selected studies in references [9-12].

2. Meta-Analysis Models

The goal of meta-analysis synthesis is to understand results of any study in the context of all other studies[1]. If the effect size is consistent across the data, we estimate the effect size as accurately as possible and investigate its robustness across all the data under review. Meta-analysis allows us to combine the summary effect for all studies and then assists us to evaluate the statistical significance of the summary effect. It will calculate the Z values to test the null hypothesis in a rigorous manner and will lead to more significant and more relevant questions regrading the findings in the data.

Two statistical models that traditionally are being used in meta-analysis include fixed effects Model described by Mantel and Haenszel[13], and random effects model developed by DerSiminian and Laird[14]. The fixed effects model assumes homogeneity of the true treatment effect and the variances around each mean effect depending on the size of each study. Whereas the random effects model includes between study differences in treatment effects while calculating the variances leading to a wider confidence interval and takes into account the heterogeneity in the treatment effect. In the work presented in this paper, it is focusing on the fixed effects model and will be describing the calculation procedure adopted for both continuous and binary data. Two different MATLAB codes were developed and validated by comparing results described by working examples in the work of Borenstien et al.[1].

3. Selection of Meta-Analysis Methods

3.1 Fixed Effects Model with Continuous Data

In this model, using the mean, standard deviation, and sample size, the bias-corrected standardized mean difference (Hedges'g) was calculated as the effect size measure. The summary size effect was then calculated to predict the confidence interval, Z value and p-values along with the variance of the true standardized mean differences. The working steps that were adopted in the MATLAB program are summarized here[1].

3.1.1 step 1

Compute the standardized mean difference for two groups: $d = \frac{\overline{X_1} - \overline{X_2}}{S_{within}}$ where $\overline{X_1}$ *and* $\overline{X_2}$ are the sample means of the two groups and S_{within} is the with-in groups standard deviation, pooled across groups (with n1 and n2 as the sample sizes for two groups)

$$S_{within} = \sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}} \quad (1)$$

3.1.2 step 2

The variance and standard errors of d are $V_d = \frac{n_1+n_2}{n_1 n_2} + \frac{d^2}{2(n_1+n_2)}$ and $SE_d = \sqrt{V_d}$ (2)

3.1.3 step 3

The bias in d is removed by a correction factor J giving unbiased estimates called Hedges' g
$J = 1 - \frac{3}{4df-1}$ where df is the degree of freedom used to estimate S_{within}. (3)

3.1.4 step 4

g, variance and standard error of g are calculated as
$g = J \times d, \quad V_g = J^2 \times V_d, \quad and \quad SE_g = \sqrt{V_g}$ (4)

3.1.5 step 5

Compute the Summary Effect by performing the Fixed- Effect meta-analysis Model
The average weight assigned to each study: $W_i = \frac{1}{V_{Yi}}$ where V_{Yi} is the with-in study variance for study (i).

3.1.6 step 6

The weighted mean is computed as $M = \frac{\sum_{i=1}^{g} W_i Y_i}{\sum_{i=1}^{g} W_i}$ (Summary Effect Size) (5)

3.1.7 step 7

The variance and standard error of the summary effect is
$V_M = \frac{1}{\sum_{i=1}^{g} W_i} \quad and \quad SE_M = \sqrt{V_M}$ (6)

3.1.8 step 8

95% lower and upper limits for the summary effect confidence intervals, and Z factors are
$LLM = M - 1.96 \times SE_M$ $ULM = M + 1.96 \times SE_M$ $Z = \frac{M}{SE_M}$ (7)

3.1.9 step 9

For one-tailed and two- tailed test the *P*-values are given by

$$p = 1 - \emptyset(\pm|Z|) \qquad and \qquad p = 2[1 - \emptyset(\pm|Z|)] \tag{8}$$

3.1.10 step 10

Estimate τ^2, the variance of the true standardized mean differences by using equations described in reference [14].

3.2 Fixed Effects Model for Binary Data

In order to incorporate Fixed Effects model for given binary data, we start with events and non-events in two independent groups that were investigated and will use either Odds Ratio or Risk Ratio as the effect size measure. The working steps that were adopted in the MATLAB program are summarized here[1].

3.2.1 step 1

Calculate Odds Ratio as

$$Odds\ Ratio = \frac{\frac{Events}{NonEvents}|_{Treated}}{\frac{Events}{NonEvents}|_{Control}} \tag{9}$$

3.2.2 step 2

Calculate Y = ln(Odds Ratio)

3.2.3 step 3

Calculate W (weight assigned to each study) and WY for each study

3.2.4 step 4

Find M (weighted mean)

$$M = \frac{\sum W_i Y_i}{\sum Y_i} \tag{10}$$

3.2.5 step 5

Find variance and standard error of weighted mean. Use equation (7) to find LL_M and UL_M.

3.2.6 step 6

Calculate Z and p-values and convert the log(Odds Ratio) and confidence limits to the Odds Ratio scale.

3.2.6 step 7

Estimate τ^2, the variance of the true standardized mean differences by using equations described in reference [14].

The roadmap for the MATLAB program in shown in Figure 1. Two MATLAB programs were developed and tested as will be explained in the next section.

4. Validation of MATLAB Programs

Both MATLAB programs developed in this study were tested against the given test cases in the reference [1]. Test results for the case of fixed effects model for continuous data are included in this paper. Six study groups were selected who performed statistical analysis on two groups (Treated and Control) for a treatment as shown in Table 1. Table 2 shows fixed effect model computation and Table 3 includes relative weight and Hedges computation that led to the conclusion. Using fixed-effect model, the standard mean difference (Hedges 'g') was found around 0.4145 with a 95% confidence interval of 0.29 to 0.54. The Z-value was 6.47, and the *P*-value was <0.0001 (one-tailed) or <0.0001 (two-tailed). These results are similar to what have been tabulated in reference [1] for these six studies thereby validating our MATLAB model that was later on used to investigate four different studies on salt intake and its impact on various health parameters. This is being explained in the next section. It is important to note that the second MATLAB model (Fixed Effect Model for Binary Data using Odd Ratio as size effect) was also tested against the given data in reference [1] and was validated. The results for this model are not included in this paper.

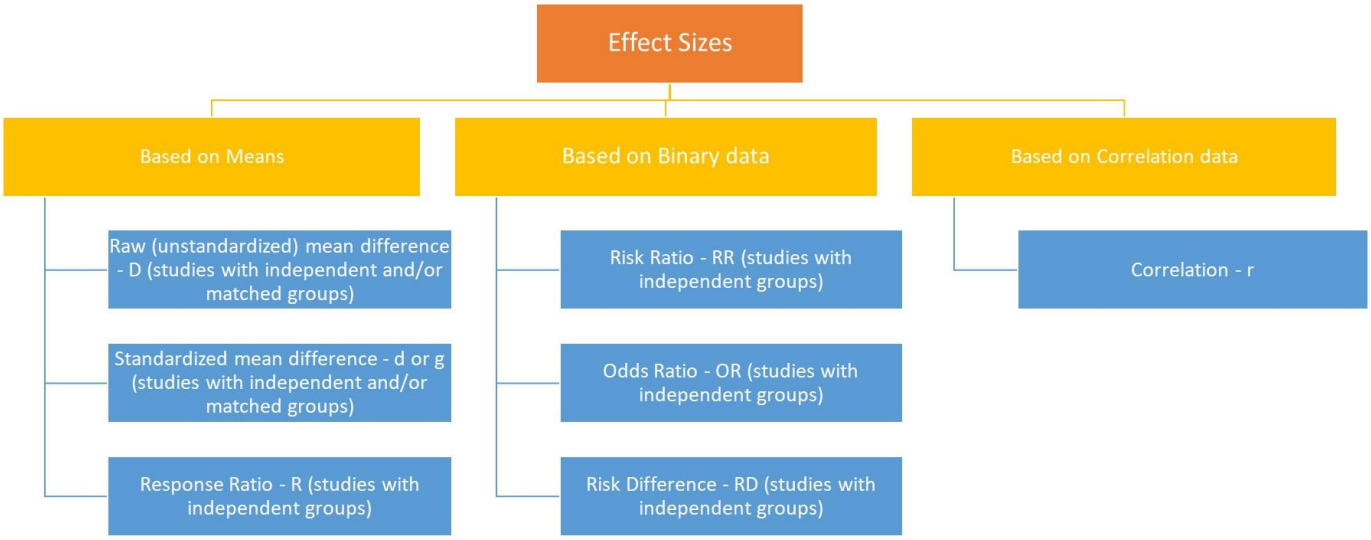

Figure 1. Road map for MATLAB program to calculate Summary Effect using the fixed-effect model

Table 1: Basic Data Obtained from Six Independent Studies [Reference 1]

Treated

Study	Mean	SD	n
A	92	20	60
B	92	22	65
C	88	26	40
D	82	17	200
E	88	22	45
F	92	22	85

Control

Study	Mean	SD	n
A	94	22	60
B	98	21	65
C	98	28	40
D	94	19	200
E	98	21	50
F	96	21	85

Table 2. Shows fixed effect model computation

Study	Y	Vr	W	WY	WY2	W2
A	0.0945	0.0329	30.3515	2.869	0.2712	921.2144
B	0.2774	0.0307	32.5681	9.033	2.5054	1060.682
C	0.3665	0.0499	20.0482	7.3486	2.6936	401.931
D	0.6644	0.0105	95.1105	63.19	41.9825	9046.013
E	0.4614	0.0405	24.72	11.4064	5.2632	611.0776
F	0.1852	0.0234	42.698	7.9062	1.4639	1823.1153

Table 3: Relative Weight and Hedges Computation

Study	Std Diff (g)	Lower Limit	Upper Limit	Relative Weight (percentage)
A	0.0945	0.2894	0.5396	12.3633
B	0.2774	0.2894	0.5396	13.2662
C	0.3665	0.2894	0.5396	8.1664
D	0.6644	0.2894	0.5396	38.7421
E	0.4614	0.2894	0.5396	10.0694
F	0.1852	0.2894	0.5396	17.3925

Figure 2. Computed standardized mean difference and 95% confidence interval

5. Preliminary data analysis

As a preliminary test case, we conducted meta-analysis on four selected studies that included data on the impact of salt intake on various health parameters. That included the work conducted by Dyer et al.[9], Radhika et al.[10], Ma et al.[11], and Yang et al.[12]. Dyer et al.[9] examined salt intake and its relationship to BMI (body mass index) and blood pressure across 52 different areas (INTERSALT). Salt collection was measured via 24-hour urine collection. Radhika et al.[10] determined the average dietary salt intake in Urban South India and compared its relationship to hypertension. Salt intake was measured via a food frequency questionnaire. BMI was a starting variable, along with waist

circumference, smoking, alcohol intake, etc. Ma et al.[10] analyzed data from the UK National Diet and Nutrition Survey 2008/2009 to 2011/2012. Salt collection was measured via 24-hour urine collection. Yang et al.[12] examined salt intake and its relationship to mortality. Salt intake was measured via 24-hour dietary recall. Meta-analysis was performed using fixed effect model for continuous data. Using MATLAB model, the standard mean difference (Hedges 'g') was found about 0.3838 with a 95% confidence interval of 0.35 to 0.41. The Z-value was 25.97, and the *P*-value is <0.0001 (one-tailed) or <0.0001 (two-tailed). These results are of very preliminary nature and need rigorous efforts to extract more meaningful information on the data collected by various researchers included here. Work is in progress and new results are being generated and analyzed using our two MATLAB models.

Table 4. Basic Data Obtained from References [9,10,11,12]

Treated

Study	Mean	SD	n
Dyer	3.496	1.545	5064
Radhika	9.9	3.9	514
Ma	8.4	0.1	519
Yang	3.5915	0.0305	2727

Control

Study	Mean	SD	n
Dyer	3.404	1.845	5010
Radhika	8	2.8	1388
Ma	6.2	0.2	266
Yang	3.657	0.0265	5333

Table 5. Computed Relative Weight and Hedges 'g'

Study	Std Diff (g)	Lower Limit	Upper Limit	Relative Weight (percentage)
Dyer	0.0541	0.3548	0.4128	54.9885
Radhika	0.6058	0.3548	0.4128	7.9118
Ma	15.3415	0.3548	0.4128	0.1404
Yang	0.7701	0.3548	0.4128	36.9594

5. Conclusions

As new data on salt-intake and its impact is being generated at a rapid rate, it is becoming important to perform met-analysis on the newly emerging data. The need to develop MATLAB programs was identified that, at a later stage, can be used as an open source analysis tool. In this study two such MATLAB models were developed. Both models were test against the data collected from reference [1] and were successfully validated. One MATLAB model was based on the Fixed Effect Model that was applied to continuous data calculating standardized mean difference and its variance. This MATLAB program was used to perform meta-analysis on salt-intake data that was collected from four different studies. Meta-analysis results are presented that indicated robustness of the technique. Further information on statistical analysis need more rigorous efforts that are currently in progress.

6. References

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