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Agricultural chemical exposure and birth defects in the Eastern Cape Province, South Africa

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ABSTRACT

A case - control study to investigate the association between pesticide exposure and prevalence of congenital malformation in women was conducted on rural women in the Eastern Cape Province of South Africa. A total of 89 cases and 178 controls were interviewed. Data on birth defects were obtained from the register of the Paediatrics Department at the Cecilia Makiwane Hospital in Mdantsane, one of the biggest referral hospitals in the province. The cases were those children who were diagnosed with selected defects during their first years of life. Controls were chosen from the same area as the cases, to ensure homogeneity in socio-economic activities of the mothers. Similar studies, which confirmed a possible existence of an association between pesticide exposure and certain birth defects, have been conducted in the developed world. This study, conducted in a rural African environment, set out to examine whether a similar association exists.

The results show statistically significant associations between pesticide exposure in gardens and fields, as well as exposure to dip through livestock dipping and the reuse of plastic containers and birth defects.

Keywords: Pesticide, garden chemicals, dipping, reused container, exposure, birth defects.

BACKGROUND

South Africa is a major pesticide user on the African continent. However detailed information on the types of pesticides used is not accessible. About a fifth of South Africa's arable land is used for agriculture. About a tenth of the economically active population is employed in the agricultural sector. Agriculture is one of the most important income generating activities and the fifth biggest employer in the country (1).

The Eastern Cape is the second largest province in South Africa, covering an area of 169 580 square kilometres. Commercial farming is characterised by use of agricultural machinery and less manpower. With the ever advancing technology pest and weed control and chemical spraying techniques have been advanced. Commercial farmers

sometimes use aerial spraying but in a lot of cases spraying is manually done. The majority of the commercial farm workers are males while women dominate the subsistence farming and vegetable gardening sector. Most sprayers in commercial farms have some informal education on the use of pesticides. Subsistence farmers are predominantly poorly educated with little or no informal education on pesticide use.

There was growing concern that the incidence of certain birth defects was increasing in the Eastern Cape province. This study therefore had as its main objective to investigate if there is any association between birth defects and pesticide exposure and in the event that it exists, establish its strength. The research hypothesis in this study was that exposure to agricultural chemicals is significantly associated with certain birth defects. A case-control study involving 89 cases and 178 controls was conducted in the area.

METHODOLOGY

Ethic Committee

The Ethic Committee of Fort Hare University has approved the study. However the study had also to be approved by the Ethic Committee of Region C and by each Clinic committee.

Study design

A pilot study was conducted in the rural area where farming was done. The results of this study showed that there are adverse health related problems in regard towards pesticide exposure. The circumstances in the particular area made it necessary to focus in the follow up study on the development of birth defects.

Data from the records at Cecilia Makiwane Hospital for the years 1998, 1999 and 2000 were analysed and there seemed to be an increase in the prevalence of birth defects treated at this hospital during these years. Random samples of cases were selected from the records. These were then visited in their homes or invited to the clinic for interviews.

Socio-economic and demographic variables were recorded for each woman. These include geographical region, age, education, marital status, number of live births, income and employment. The women were also classified, regarding the use of garden chemicals, keeping of domestic animals and type of water container they use for fetching and storage of water for household use and birth defect status as a response.

A questionnaire was designed and used as the principal method of data collection for the study. The nurses were briefed about the purpose of the study and trained in administering the questionnaire. The nurses obtained oral consent from each mother interviewed.

Definition of cases

Cases were chosen from the Hospital register of the Department of Paediatrics, on the basis of ICD IX codes for birth defects. These defects have been suspected of being associated with exposure to some pesticides. The ICD IX codes used considered for this study are given in Table 1 below.

Table 1: ICD IX Birth defects

ICD – Code	Disease
740.0 - 742.9	Nervous system defects
745.0 - 747.9	Cardiovascular defects
749.0 - 749.2	Oral defect
752.6	Epispadia or hypospadias
754.0 - 754.9	Clubfoot
756.9	Musculoskeletal defects
759.7 - 759.9	Unspecified defects

Definition of controls

The controls were defined as those children born in the same area as the cases, but without visible malformations and otherwise healthy. These were identified by clinic nurses who also assisted with the interviews. The mothers of the cases and controls were interviewed either at their homes or in their nearest clinic.

Exposure assessment

To assess exposure to pesticides, questions about activities in and around the house were included in the questionnaire. Both the cases and the controls were asked the same questions. The South African winter season is generally not as severe as it is in the Northern Hemisphere and therefore harvesting is possible throughout the year.

Most mothers interviewed said they were unemployed. However, they contribute to the family income by working in their own gardens and fields. In these gardens and fields, the women are exposed to pesticides. The livestock, like cattle, goats or sheep are regularly dipped as a tick control measure. The dips used are known to contain Flumechin. Dipped animals were therefore considered as another source of pesticide exposure.

Another source of exposure in the study population was the reuse of plastic containers, which had been previously used for the storage of agricultural chemicals. These containers were used for fetching and storing of water.

STATISTICAL ANALYSIS

The statistical analysis was carried out using Epi-Info 6 and SAS statistical software packages. The analysis was carried out according to type of exposure. Exposure to garden chemical spraying, animal dipping and through water container, are the three types considered in this study. Water containers were classified as tapped water, plastic container and metal container. Chemical exposure was compared against non-chemical exposure and animal exposure was compared against non-animal exposure. In the same way the plastic container was found to be significantly associated with birth defects. Further analysis to determine the association between use of plastic containers originally used for agricultural chemical storage for storing water and birth defects was also carried

out. In the same way associations between birth defects and exposure to individual chemicals and animals was also assessed.

With birth defect as the response variable logistic regression of birth defect on the different types of exposure was used as the principal method of analysis resulting in three different models depending on the type of exposure. All tests were performed at a 5% significance level.

RESULTS

Socio-economic background

Age groups. The ages of the mothers in this study ranged from 14 to 51 years. The ages of the mothers in the control group ranged from 14 to 48 years while for the cases they ranged between 18 and 51 years. About 7 percent of the women could not remember their dates of birth. Of all the women interviewed, 62 percent were single mothers and had no knowledge of the whereabouts of their children's fathers.

Education and Income. Generally the mothers of cases were less educated than those of the control group. Information on income was considered unreliable since most of the mothers were unemployed, at least formally. However quite a good number of them sell products on the market and earn an inconsistent income from this.

Water source, transportation and storage. The women use different sources of water and store it differently. Only 18 percent of the mothers have access to tapped water inside

the house. The majority of women used water outside the house, like a communal tapes and water from rivers, dams and rain tanks.

Agricultural chemical exposure analysis

Logistic regression of birth defect, as the response, on type of water container, exposure to agricultural chemicals, keeping of domestic animals and the socio-economic or demographic variables was performed. These analysis showed that birth defects were not significantly associated with all the demographic variables used. Agricultural chemicals, exposure to dipping domestic animals and type of water container had statistically significant associations with birth defects. These three variables were then separately analysed giving the following results.

Domestic animals. Of the 267 women in the study population 172 kept domestic animals. Nearly 60 percent of the cases kept animals while in the case of controls 68 percent kept animals. Only "big" animals like cattle, goats and sheep need dipping. Small animals are not normally dipped and therefore do not appear in the analyses. Only the cattle, goats and sheep were considered in further analysis. Information obtained about the chemical contents of the dip used showed that it contained Flumechin a pesticide used to kill ticks and tsetse flies. Exposure to dip was assessed through exposure to domestic animals. The overall exposure to domestic animals was found to be statistically significant with an odds ratio of 1.92, a 95 % confidence interval of (1.15 – 3.14) and a p-value of 0.01.

Only 36.3 percent of these animals were regularly dipped. About 48.3 percent of the cases were involved in dipping, compared with 30.3 percent of the controls. Exposure to cattle was found to be significantly associated with birth defects while exposure to goats and sheep were not significant at a 5% level. The results of the analysis are shown in Table 2 below.

Table 2: Association between animal exposure and birth defects.

Animal	Odds Ratio (OR)	95% CI of OR	p-value
cattle	2.53	1.40 – 4.70	0.0014 *
goats	1.18	0.78 – 3.95	0.7650
sheep	0.74	0.10 – 4.11	0.7180

** statistically significant*

Therefore the statistical significance of exposure to domestic animals was due to cattle only since exposure to both goats and sheep are not statistically significant.

Water container. Three types of containers used for the storage of household water were identified in this study, namely, tap water, plastic container and metal container. The analyses of these containers showed that women who use metal containers and tapped water are at an equal risk of having a defective child. However the use of plastic containers is significantly associated with birth defects. Women who used plastic containers were about six times as likely to have defective babies as those who used tap water or metal containers. In a closer analysis of the plastic containers it was found that women who use containers originally used for the storage of agricultural chemicals were

about two times more likely to have defective babies than those who did not. The results of these analyses are shown in Tables 3 and 4 below.

Table 3: Logistic regression results for birth defect on water container

Parameter	DF	Estimate	Standard error	Chi-square	p-value
intercept	1	-1.3045	0.2401	29.5248	0.0001*
tap	1	0.0517	0.3170	0.0266	0.8704
plastic	1	0.9125	0.2551	12.7922	0.0003*

- *statistically significant*

Table 4: Odds ratios for water container and reuse of plastic containers

Containers	Odds Ratio (OR)	95% CI of OR
Tap vs Metal	2.762	0.761 – 13.179
Plastic vs Metal	6.530	2.217 – 27.954*
Reuse vs Non-reuse	1.873	1.196 – 3.201*

- Statistically significant

Garden chemicals. Most of the mothers were involved in vegetable gardening and subsistence farming, though at a small scale. About 80 percent of cases and 74 percent of controls were actively involved in gardening and farming. The use of pesticides and garden chemicals was confirmed in 60 percent of the cases and 12.4 percent of the controls. The most commonly used garden chemicals and soil additives

are insecticide, organophosphate and Blue Death. "Blue death" is a mixture of three different chemicals, these are Carbaryl, Carbufuran and Camphechlor. The latter has been banned in South Africa since 1970 (Department of Agriculture 1999). The distribution of pesticide use in the study population is shown in Fig 1 below.

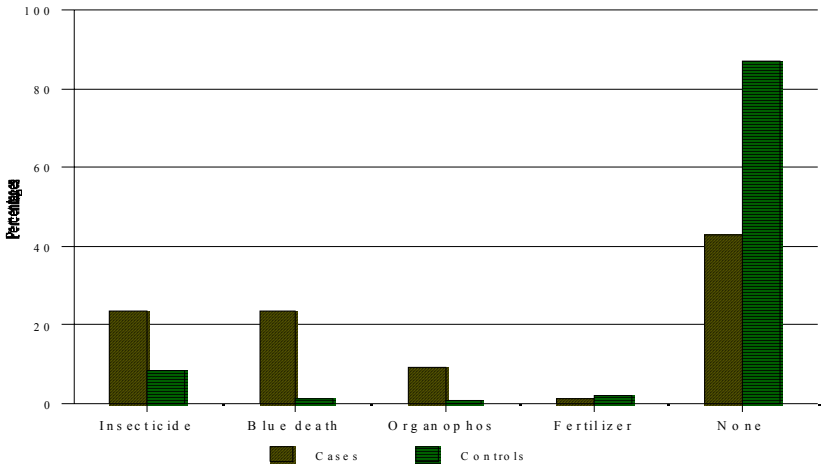

Fig 1: Distribution of pesticide use by type of agricultural chemical

The use of garden chemicals showed a significant association when compared against non-use of such chemicals. Women exposed to garden chemicals are about seven times as likely to have defective babies as those not exposed to them.

The garden chemicals were further analysed and it was found that women using fertilizer and insecticides were equally likely to have defective babies as those not using any garden chemicals at all. However the women who were exposed to pesticide, 'blue death' and organophosphate were at a higher risk of having defective babies than those exposed to insecticide, fertilizer or nothing. The women exposed to pesticide, 'blue death' and organophosphate are more than six times as likely to have defective babies as those exposed insecticide, fertilizer or nothing.
The results of this analysis are shown in Table 5 below.

Table 5: Odds ratios for exposure to garden chemicals

Chemical	Odds Ratio (OR)	95% CI of OR
chemicals vs nothing	7.181	3.990 – 13.249*
pesticide vs nothing	6.000	2.751 – 13.489*
fertilizer vs nothing	1.026	0.052 – 7.186
insecticide vs nothing	4.105	0.480 – 35.097
blue death vs nothing	9.105	4.954 – 17.879*
organophosphate vs nothing	7.842	5.778 – 12.627*

** statistically significant*

These results show that there is a statistically significant association between birth defects and exposure of the mothers to different agricultural chemicals. Exposure through use of plastic containers previously used for storage of agricultural chemicals for storing water meant for household uses and through use of garden chemicals and cattle were the three forms of exposure that were significantly associated with birth defects. All the socio-economic and demographic variables included in the analysis were not significantly associated with birth defects.

DISCUSSION

Most studies on the use of pesticides focus on people who have been occupationally exposed to pesticide. Occupational exposure is much easier to determine, since the kind of exposure and the duration is fairly accurately known. These studies on occupational exposures tend to consider male exposure, rather then female exposure. Studies on pesticide exposure on females and the consequences of adverse effects on reproductive health are less frequent. There are only few studies in the late 1960's and most studies have been done during the 1990's (3). Many studies have shown the possible influence of pesticide exposure and adverse reproductive outcomes. These studies covered maternal, paternal or both parents' occupational exposure, and examined congenital malformation (4, 5, 6 and others) miscarriages (7) and stillborn babies due to congenital malformation after pesticide exposure had occurred (8, 9).

Most studies of pesticide exposure have been conducted in the developed world. Only a few studies have been undertaken in the developing world (10). Some of the studies have

been undertaken in South Africa, in the Western Cape (11, 12, 13, 14). However all of these studies have focused on occupational exposure and mainly on male workers. A study in Columbia (15), which focused on couples, male and female workers and their reproductive health is one of the very few of such studies carried out in a developing country. Studies on agricultural chemical exposure and the adverse reproductive outcomes have mainly been undertaken in the developed world. (16, 17, 18, 19, 20, 21).

All these studies were meant to meet the "ideal" study situation, such as, married couples, the exact knowledge of kind of pesticide used and duration of the exposure and the fact that the couple had decided to conceive a child. There are data available of the father's activity and whether the husband or the wife or both of them had been exposed to some kind of chemical as well as time of possible exposure occurred. The couple was aware of the danger associated with pesticide exposure.

The couple, both of them, were highly literate. The exact information about time to pregnancy was available and possible early loss of pregnancies were noticed.

In a rural Third World environment these conditions are very different. In this study an attempt has been made to establish an association between chemical exposure and birth defect outcome, without any of the above mentioned conditions. In this study nearly 62 % of the mothers were single and more then 58 % did not follow an occupation outside their homes. The exposure assessment had to be taken from the women's activities, like gardening, fieldwork and dipping of livestock. A pilot study, undertaken in the area

showed differences in the behavioural pattern between those people who were occupationally exposed to pesticides and those who used pesticides privately (22).

Within this study it was possible to link chemical exposure to the outcome. It has been possible; to show that there is a relationship between certain chemical exposures and adverse reproductive outcomes. The results of this study show that there is an association between pesticide exposure and birth defects, confirming the findings of similar studies carried out in the developed world.

Due to the relatively small numbers the results of this study may not be conclusive.

There is, therefore, a need for more studies, which are broader, larger in terms of the number of women under study and more variables. Such variables could be a combination of analyses of ground water, analyses of food, to confirm residues in food. Prevention of these birth defects is possible and everything should be done to reach this goal.

CONCLUSION

There is an urgent need for an awareness campaign with regard to the use of pesticides since many women are not aware of the danger of using chemicals. The same applies for the reused plastic containers for fetching water. Workers are included in many education programmes on pesticide use, however these women who care for the food of their families are in most cases left out (23).

Organic Farming

It is necessary to develop alternative farming methods. Chemical products are regarded by proponents of organic methods as injurious to health and the environment and are unnecessary for successful cultivation (24).

Water Storage

The accessibility of water is a huge problem in all rural areas in Africa. If water needs to be fetched from an outside tap, rain tank, river or dam a container will be needed. The women in our study are so poor that they use any container available. A possible way of solving the problem is to charge a deposit on the containers, refundable on return of the container. Users would therefore be persuaded to return the containers for safe disposal. Another suggestion might be that any female living on her own in rural settlements should be supplied with a water container, which is safe to use for fetching and storing water.

Birth defects monitoring system

A national birth register should be established. This register should contain any available information on the child; date of birth, gestation age and weight and in case of a defect the ICD Code. On the parents there should be information such as occupation and place of residence of both parents, if possible up to three months prior to conception, as well as socio-economic data.

Acknowledgement

We wish to thank the Department of Paediatrics at Cecilia Makiwane Hospital for the permission to analyse the data in regard of birth defects. We also wish to thank all nurses involved in the interviews and finally all mothers who took their time and effort to come to the clinics to be interviewed. The University of Fort Hare for supporting the study.

July 2003
Reviewers' reports

Agricultural chemical exposure and birth defects in the Eastern Cape Province, South Africa

Report from Ruth Etzel:

Major:

1. In the Abstract, please provide the odds ratios and 95% confidence intervals for the major findings of the study.

2. In the Background section, please give the reader an indication of the socioeconomic circumstances of the people who were involved as participants in the study. I am assuming that they were *very* poor women. Can you provide same aggregate data about income in the community to give the Western reader a better sense of who the participants were?

3. I would like to see an additional table showing a comparison of the following factors among cases and controls: age, race, education, marital status, number of live births, etc.

4. On page 4, please clarify whether all birth defects during 1998 – 2000 with the codes listed in Table 1 were included in the study.

5. On page 5, please clarify whether the controls were matched by year of birth.

6. Please help the reader to understand the frequency of livestock dipping. Does it occur once a month or once a year?

7. Please explain how a woman might get exposed while dipping an animal. Do her clothes get thoroughly wet? Do the women wear any gloves or other barriers?

8. Was maternal use of tobacco evaluated in this study?

Minor:

9. On page 3, please reword the sentence regarding the Ethics Committee. I suspect that you meant to say that the study was approved by the Ethics Committee of Region C and by each Clinic committee.

10. On page 3, please describe what circumstances in the particular area made it necessary to focus on birth defects.

11. On page 9, please change “defective babies” to “babies with birth defects”.

12. On page 13, please change “follow an occupation outside their homes” to “work outside the home”.

Level of Interest:
A paper whose findings are important to those with closely related research interests

Report from Rubina Imtiaz:

Major/General Comments:

1. The manuscript needs to be reorganized to clearly state the background, objectives, methods, analyses, results and discussion parts without the overlap and repetition that is currently seen. For example, a pilot study is mentioned in the methodology heading under Study Design. It is not clear where the pilot study ends and the subsequent study begins. If indeed, these are two separate studies (i.e. the pilot led to a full-fledged, subsequent study) then the pilot study needs to be briefly described under background and the main body of the paper should be dedicated to the larger study.

2. Methodology: This section needs to add critical information on how the study design, study population (or the hospital from which it was derived) and sample size were determined. What was the case definition and what were the criteria for control selection (by the nurses). What were the potential biases/confounders and how were they countered? Not sure what authors mean by "cases were chosen from the hospital register...., on the basis of ICD 9 codes for birth defects". It would be good to mention what and why, particular birth defects were selected as outcomes. Controls are described as "those children born in the same area as the cases but without the visible malformations and otherwise healthy" . This would exclude certain CVS and CNS birth defects mentioned in the table.

3. It would be helpful to have the questionnaire appended, or, key questions may be abbreviated in the methods to highlight what exposures were considered.

4. Not clear what routes of exposure, timing of exposure (throughout pregnancy, period before and during pregnancy, etc.) were studied as related to association with birth defects.

5. How many interviewers were used and interviews were conducted over what period of time relevant to delivery of the child (was it comparable between case- and control-mothers?).

6. Cases and controls are different from the interviewees in this study (case-mothers and control-mothers?) but are referred to similarly. Need to correct the language to reflect this.

7. Statistical Analysis: large parts of this section are not clear and critical information is missing which does not allow the validation of reported results. It would be easier

for the reader to comprehend and for the authors to present analyses starting with descriptive methods (categories and groups studied), bivariate analyses and THEN move to regression analysis (what was the indication for using this? How was the study population stratified for various tests? Maybe best to show this in 1 or more tables with actual numbers in each cell rather than just percentages which can be misleading in smaller strata). The tests of significance used and confidence intervals and/or p values should be shown for each sub-group (again; recommend a table). As it stands now, this part of the manuscript is pretty unintelligible.

8. Results: Recommend following the scheme mentioned above (descriptive, bivariate, multivariate). Please show the actual numbers with the percentages. Under Education and Income, rather than using subjective language, recommend using actual numeric results (levels of grade studied by case- vs. control-mothers) with means or medians for each group of mothers. Same for other results.

9. Not clear what definitions were used for "exposure", e.g. for dipping: was a woman considered "exposed" if she ever dipped an animal during pregnancy, or dipped an animal certain number of times a week, etc. Was this kind of "dose" relationship considered in this study or controlled for?

10. Table 2 needs to show the exposure (is it the type of animal or activity leading to exposure?) and the birth defects (numbers and percentages in each row and column) and then the OR, CI, p-values, etc. It also needs to clearly mention the statistical test used.

11. On page 9, under water containers, there is a confusing comparison of risk in two groups of women (using tap water and using metal containers). Other parts of the manuscript indicate that women who used tap water did not have a risk of birth defects. Which one is correct? Again: this can be presented much better in a table with numbers using different sources/containers of water, with and without adverse birth outcomes.

12. All tables need major improvement to clearly make the point. Simply copying SAS results in a tabular form without proper headings or labels will not accomplish this.

13. Discussion: What was the nutritional status of the studied women during pregnancy? This may be a big confounder as certain deficiencies are strongly associated with certain birth defects (folic acid deficiency and NTDs). Other limitations of the study need to be discussed and how they were met.

14. The Conclusion part is really "Recommendations".

This is a paper whose findings would be important to others involved in health outcomes research in farming communities in developing countries, once the facts are presented in a replicable, sound manner.

Report from Colin Soskolne:

1. Consistency in the use of the word "pesticide" and "pesticides" (plural). I believe that the latter is what is intended throughout. [MINOR]

2. It should be made clear whether matching was done (I believe it was). In fact, I believe that the matching of 2 controls to each case on the single matching variable of being born in the same area within about 6 months of the case took place. If so, then the appropriate statistical method to use is: conditional logistic regression. These points ought to be made clear in the paper. [MAJOR]

3. In the "Statistical Analysis" section, the last five lines of the first paragraph do not seem to me to be describing the statistical analysis, but rather the results. This needs to be clarified. [MINOR]

4. On page 9, Table 3 presents logistic regression results in a format with which I am unfamiliar. Is it correct? [MINOR OR MAJOR?]

5. On page 11, the 4th - 7th lines are duplicated sentences and ought to be merged into one sentence. [MINOR]

6. On page 13, I disagree with the final sentence (one liner) in the last full paragraph. [MINOR]

7. On the top of page 14, ... more variables? For what? To better control potential confounding? Please clarify. [MINOR]

Level of interest

Once improved, an exceptional paper that breaks new ground and has implications well beyond its field. I believe that this type of research, and this paper in particular, could have profound impacts for improved public health and ought to be encouraged.

Comments from the Editor:

i. On p. 6 you need to describe <u>how</u> controls were selected by clinic nurses. On the same page please indicate if the interviewers were blind to the case or control status of the person they were interviewing (I assume not).

ii. On p. 11 you say women who use metal containers were at “low” risk of having a baby with defects. It is only low compared to the other mothers, not absolutely low. Your data do not tell you what their absolute risk was.

iii. On p. 11 you also say that use of metal containers and tap water were not statistically significantly associated with birth defects. However your Table 7 is metal containers *versus* tap water, and in fact shows use of metal containers with an OR of 2.76, which is markedly increased. True, it is not statistically significant, but this might be because of small numbers of subjects. You cannot conclude that there is no association of metal versus tap, as you seem to.

iv. On p. 13, lines 3 – 5: This statement does not seem correct to me. Women exposed to pesticides have more than 6 times the odds of women who were *not* exposed, not 6 times those exposed to insecticide or fertilizer. If I read this wrong, then you need to either adjust the text or the table.

v. p. 15, first full sentence at top of page (beginning, "A pilot study,…"). I have no idea what this sentence means. Please clarify.

vi. p. 16, last paragraph: I think this could be omitted as it does not follow from the paper and seems weak. The previous paragraph sums up the significance of the findings and contains some good, paper-specific recommendations.

vii. You describe the limitations and difficulties of doing such a study in the developing world. Perhaps you might change your title to reflect the tentative nature of your effort, changing the subtitle (after the colon) to :A Case-Control Pilot Study.