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Do Sex and Atopy Influence Cough Outcome Measurements in Children?

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Background: Despite the commonality of cough and its burden, there are no published data on the relationship between atopy or sex on objectively measured cough frequency or subjective cough scores in children. In 202 children with and without cough, we determined the effect of sex and atopy on validated cough outcome measurements (cough receptor sensitivity [CRS], objective cough counts, and cough scores). We hypothesized that in contrast to adult data, sex does not influence cough outcome measures, and atopy is not a determinant of these cough measurements.

Methods: We combined data from four previous studies. Atopy (skin prick test), the concentration of capsaicin causing two and five or more coughs (C2 and C5, respectively), objectively measured cough frequency, and cough scores were determined and their relationship explored. The children's (93 girls, 109 boys) mean age was 10.6 years (SD 2.9), and 56% had atopy.

Results: In multivariate analysis, CRS was influenced by age (C2 coefficient, 5.9; $P = .034$; C5 coefficient, 29.1; $P = .0001$). Atopy and sex did not significantly influence any of the cough outcomes (cough counts, C2, C5, cough score) in control subjects and children with cough.

Conclusions: Atopy does not influence important cough outcome measures in children with and without chronic cough. However, age, but not sex, influences CRS in children. Unlike adult data, sex does not affect objective counts or cough score in children with and without chronic cough. Studies on cough in children should be age matched, but matching for atopic status and sex is less important.

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Abbreviations: C2 = concentration of capsaicin required to stimulate two or more coughs; C5 = concentration of capsaicin required to stimulate five or more coughs; CRS = cough receptor sensitivity; QOL = quality of life; VAS = visual analog scale

Cough is the most common symptom of respiratory disease and causes substantial burden to parents of children with chronic cough.¹ Pediatricians have long advocated that children should be managed in accordance to child-specific treatments. Indeed, in the area of cough, substantial differences between children and adults have been shown in underlying etiologies for cough and cough receptor sensitivity (CRS).^{2,3}

Assessments of outcomes are important in the clinical setting, particularly in research. Important outcomes for assessing interventions for cough include objective outcomes (cough counts and CRS) and subjective measures (cough score and quality of life [QOL]).^{4–5} We have shown previously that in children, CRS has a significant but modest relationship with cough frequency and that subjective cough scores have a stronger and consistent relationship with objective cough counts.² Adult studies later confirmed the

relationship and further showed that cough-specific QOL correlated with objective cough counts.⁹ In adults with chronic cough, objective cough counts and CRS were higher in women than in men.^{10,11} In young or prepubertal to early pubertal children, sex does not influence CRS.^{12,13} However, there are no published data, to our knowledge, regarding the influence of sex on other commonly used outcomes (cough score, objectively measured cough counts). CRS, a useful research tool, is higher when cough is present^{8,12} and decreases when cough is treated and resolved.¹⁴

Another factor that possibly influences CRS is atopy status. Atopic cough is described in some populations,¹⁵ and others have advocated allergy testing in some children with chronic cough.¹⁶ However, there are surprisingly very little data on whether atopy influences CRS or other cough outcome measures, with only four studies (all in adults) having examined

atopy and CRS. Pecova et al^{17,18} reported that adults with atopic dermatitis and allergic rhinitis had increased CRS, whereas others reported that atopy was not a determinant of CRS in adults without cough¹⁹ or with chronic cough.²⁰ Fujimura et al¹⁹ specifically studied the influence of atopy on CRS, whereas Park et al²⁰ examined (secondary analysis) whether atopy is a potential confounder in a multiple logistic regression. To date, however, there appear to be no data on the effect of atopy on other important cough outcomes (objective cough counts and subjective cough indices) in adults or children. Furthermore, it remains unknown whether atopy influences CRS in children. Although it may appear logical that atopy would not influence these other cough outcome measures (as limited data show that atopy has no effect on CRS), the mismatch between CRS and cough-specific QOL score has been documented. Using the Cough QOL questionnaire, French et al^{21,22} described a significantly higher burden in women than in men, but Kelsall et al,¹⁰ who used the Leicester QOL questionnaire, found that the effect of sex was absent. Understanding the relationship between these variables would promote better evaluation of cough and possibly a mechanistic understanding of cough.

Combining data from our various published^{4,23,24} and unpublished studies, we determined the effect of sex and atopy on various validated cough outcome measurements (CRS, objectively measured cough frequency, and cough scores) in 202 children with and without chronic cough. We hypothesized that in contrast to adult data, sex does not influence cough outcome measures, and atopy is not a determinant of these cough measurements in children.

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MATERIALS AND METHODS

Subjects

Children included in the data set for the present study were from several studies (Fig 1) as follows: control subjects and subjects from a study examining cough frequency and subjective cough (study a),²³ children with cough from a randomized controlled trial (study b),⁴ control subjects and subjects from a study that evaluated cough to asthma exacerbation (20 with asthma, eight control subjects) (study c),²⁴ and an unpublished study (children with cough and control subjects) evaluating the relationship between cough and exercise (N = 45) (study d). For the data set, additional control subjects recruited but not integrated in previous publications related to studies a to c were included, and some participants who were in both studies a and b were included only once (total of 128 from these two studies). Most of the children in the control group were studied at their school and were not excluded if they had a recent respiratory infection.²³ In study c, CRS during baseline (noncoughing state) was used for the total group, and a cough meter was not applied. Otherwise, the children underwent a skin prick test, had cough meter recordings (for objective cough counts) taken for 24 h, kept a subjective cough diary,²³ and underwent a capsaicin CRS.²⁵ Six allergens (cat pelt, dog dander, house dust mix, rye grass, grass mix, mold mix) and control subjects (histamine and diluent) were used for the skin prick test, as previously described.⁴ Atopy was defined as the presence of a wheal of ≥ 3 mm more than the negative (diluent) control subject to one or more allergens.

For each study, informed consent was obtained. Each study was approved by the respective hospitals' Ethics Committee on Human Research (Royal Children's Hospital, Melbourne, Victoria, Australia, for studies a and b; Mater Children's Hospital, Brisbane, Queensland, Australia, for study c; and Royal Children's Hospital, Brisbane, Queensland, for study d). No reference numbers were provided.

Cough Outcomes

The same method of capsaicin CRS testing for children was used²⁵ in all the studies. Briefly, capsaicin (Sigma-Aldrich Pty Limited; Castle Hill, New South Wales, Australia) was delivered through a nebulizer, controlled by a dosimeter (Mefar MB3; Air Liquide Medical Systems SPA; Bovezzo, Italy) in a configuration that allowed regulation of the inspiratory flow and pattern. Normal saline and diluent controls were given before doubling concentrations of capsaicin (1.23-1,250 μ mol) were inhaled. The number of coughs in the subsequent 30 seconds was counted by an independent observer. CRS measures were the lowest concentration of capsaicin required to stimulate two to four coughs (C2) and five or more coughs (C5).

The cough meters used were a validated ambulatory cough meter²⁶ that continuously records simultaneous electromyogram and acoustic signals for 24 h or a digital voice recorder.²⁷ All coughs were manually counted by an observer blinded to the child's clinical status. Some children from study d did not have 24-h monitoring. Thus, data were adjusted for 24 h.

Parents subjectively rated the severity of their children's cough using on a visual analog scale (VAS) from 1 (no cough) to 10 (presence of the most severe cough). We have previously shown that the VAS is related to objective cough counts²³ and a validated pediatric cough-specific QOL score.^{6,27}

Statistical Analysis

Cough frequency, VAS score, C2, and C5 were log₁₀ transformed because the data were skewed. One-way analysis of

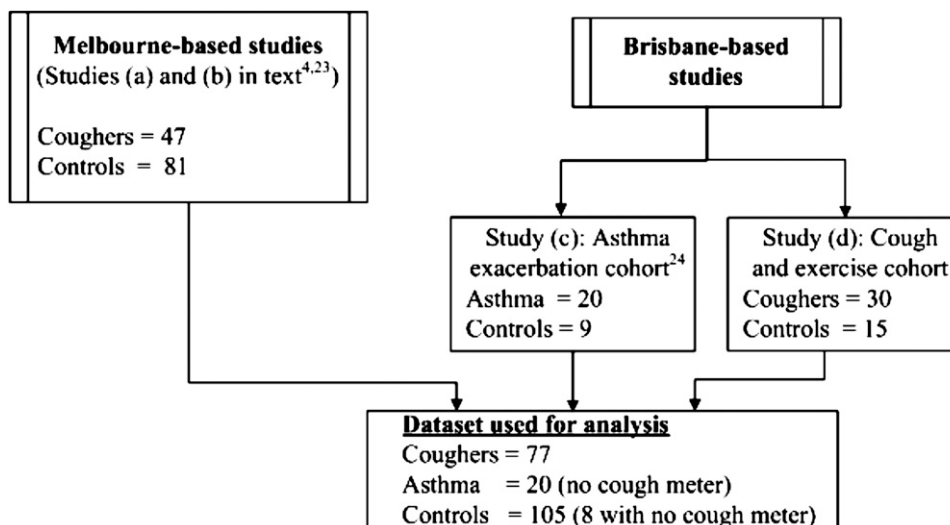


FIGURE 1. The four studies from which the current data set was drawn.

variance was used to examine the difference between groups (with Bonferroni correction). Categorical values between groups were examined using χ^2 test. Multiple linear regression was used to examine the various cough outcomes (cough frequency, VAS score, C2, and C5) as the dependent variable, with age, atopy, and sex as the independent factors. Use of regression was not intended to define a model but to assess the relationship adjusting for age because there was a significant difference between groups for age (Table 1). SPSS software (SPSS Inc; Chicago, Illinois) was used for statistical analysis, and a two-tailed $P \leq .05$ was considered significant.

RESULTS

A total of 202 children were included in the present study (105 control subjects, 20 children with asthma, and 77 children with cough). For the entire group (93 girls, 109 boys), the mean age was 10.6 years (SD 2.9), and 113 (56%) had atopy. The respective

group data (Table 1) showed significant differences between control subjects and children with cough with respect to age, CRS (C2 and C5), cough counts, and VAS cough score but no difference in atopy. Compared with control subjects, children with asthma were more likely to have atopy and had a lower VAS cough score, but other cough outcomes were similar between groups.

Cough Outcomes, Sex, and Atopy

Entire Cohort: In univariate analysis for the entire cohort, there was a significant difference between boys and girls for VAS cough score ($P = .04$) and C5 ($P = .034$) but not for C2 or cough counts. There was no difference in any cough outcomes between children grouped by presence and absence of atopy (data not shown, $P = .26-.87$). Given the significant difference

Table 1—Demographics and Cough Outcomes in the Three Groups of Children

Variable	Control Subjects (n = 105)	Subjects With Cough (n = 77)	Subjects With Asthma (n = 20)	P Value (Entire Group)	P Value ^a	P Value ^b	P Value ^c
Girls (boys)	51 (54)	36 (41)	6 (14)	.319	.808	.126	.178
Age, y	11.1 ± (2.9)	9.8 ± (2.8)	10.6 ± (3.1)	.032	.027	.958	1.0
Atopy, No. (%)	51 (48.6)	42 (55.3)	19 (95)	.001	.332	.0001	.001
Cough counts per 24 h	4.4 ± (19)	59.0 ± (6.9)	NA	.0001	NA	NA	NA
C2	15.2 ± (3.4)	8.9 ± (3.9)	16.1 ± (3.7)	.036	.045	1.0	.272
C5	67.6 ± (4.2)	34.0 ± (4.9)	94.6 ± (4.1)	.004	.011	1.0	.032
Cough score	1.5 ± (1.9)	3.1 ± (1.8)	1.0 ± (1.0)	.0001	.0001	.01	.0001

Data are presented as mean ± SD or geometric mean ± SD (for C2, C5, and cough score), unless otherwise indicated. Significant values appear in boldface type. C2 = concentration of capsaicin required to stimulate two or more coughs; C5 = concentration of capsaicin required to stimulate five or more coughs; NA = not applicable (the asthma group did not have objective cough recordings).

^aPost hoc test (control subjects vs subjects with cough).

^bPost hoc test (control subjects vs subjects with asthma).

^cPost hoc test (subjects with cough vs subjects with asthma).

in age between groups, the influence of sex and atopy cough outcomes (VAS, cough counts, C2, and C5) were examined using stepwise multiple linear regression. For all the cough outcomes, both sex and atopy were nonsignificant factors (Table 2). For CRS (C2 and C5), age was a significant factor ($P = .0001$) (Fig 2). R^2 value was small for all cough outcomes, and F test was significant only for C5.

Subgroups: When divided into groups (children with cough, children with asthma, and control subjects), the only significant factor was age for C2 and C5 in children with cough (for C2, $\beta = 11.5$; SE, 5.5; $P = .039$; and for C5, $\beta = 41.7$; SE, 11.4; $P = .0001$). Sex and atopy were not significant factors for the children with cough. For other groups and other cough outcomes, all factors were nonsignificant (data not shown). There were too few children ($n = 42$) aged ≥ 13 years (ie, likely late puberty stage¹³) to subgroup children in accordance with these age categories. The scatter of C5, VAS, and objective cough counts for children based on sex and atopy, respectively, are shown in e-Figures 1 and 2.

DISCUSSION

In 202 children with and without cough, this study shows that sex does not influence objective cough counts or validated subjective cough scores in children. Our study has confirmed that in predominantly prepubertal children, CRS is not influenced by sex. Additionally, we show that atopy has no impact on cough outcome measures (CRS, objective cough counts, and VAS score).

Some pediatric epidemiology and clinic-based studies have described increased atopy in children with cough,^{28,29} whereas others have not.³⁰⁻³² Clough and colleagues²⁹ described that atopy was associated with a greater respiratory symptom chronicity, including cough. To date, there are no published data to our knowledge on the relationship between atopy and objectively measured cough frequency or subjective cough scores in children. The present findings in this relatively large cohort of children found no asso-

ciation between atopy and any of the cough outcomes. If atopy itself causes cough, that is, atopic cough exists in children (as opposed to being a confounder), a positive association arguably would be found as described in adult studies on CRS and sex^{9,10}; for example, women have increased CRS, and cohorts consistently describe predominance of women in adult cough clinics.^{10,22} The present findings concur with studies that did not find a preponderance of atopy in children with chronic cough when other confounders, such as wheeze, are controlled for.^{31,32} Thus, the lack of association is not surprising when examined systematically. Both atopy and chronic cough are common, and a chance association is high when two items are common. Indeed, in a cohort of Australian children with chronic cough, the probability of finding an association is $\sim 40\%$ [0.4 (probability of allergic sensitization in Australian children³³) $\times 1$ (probability of having cough)]. The importance of the present findings is to negate the promotion for atopy testing or treatment of atopy,^{15,16} such as allergic desensitization or antihistamines for children with isolated chronic cough, which is further supported by data from a Cochrane review showing no significant effect of antihistamines for chronic, nonspecific cough in children.³⁴ In fact, in the safety studies on second-generation antihistamines, children with allergic rhinitis randomized to the active arm showed a nonsignificant increased risk of developing cough (OR, 1.47; 95% CI, 0.86-2.49) (Fig 3).³⁴

The lack of influence of sex on CRS in young children has been described previously by two groups.^{12,13} Varechova and colleagues¹³ further described that sex did not influence CRS of pubertal and early pubertal children (predominantly children aged < 14 years), but in late-pubertal children, CRS was increased in girls compared with boys, as described in adults.^{9,11} The present study further has found that sex does not influence objective cough counts or subjective cough scores, which is in contrast to adult data showing that sex significantly influences objective cough scores.¹⁰ Thus, although data on CRS exist, those for objective cough counts or subjective cough scores have not been described previously in children.

Table 2—Multivariate Analysis Data

Cough Outcome	Age			Sex			Atopy			Adjusted R^2	P Value for F Test
	B	SE (B)	P Value	B	SE (B)	P Value	B	SE (B)	P Value		
C2	5.9	2.7	.034	-20.0	17.0	.242	6.9	17.0	.682	0.02	.091
C5	29.1	7.4	.0001	-54.9	45.3	.227	29.5	45.1	.514	0.07	.001
Cough counts	3.9	9.2	.674	-56.8	56.0	.312	9.8	55.7	.860	-0.012	.717
VAS score	-0.51	0.05	.275	0.51	0.31	.096	-0.25	0.31	.424	0.015	.117

B is presented as an unstandardized coefficient. Significant values appear in boldface type. VAS = visual analog scale. See Table 1 legend for expansion of other abbreviations.

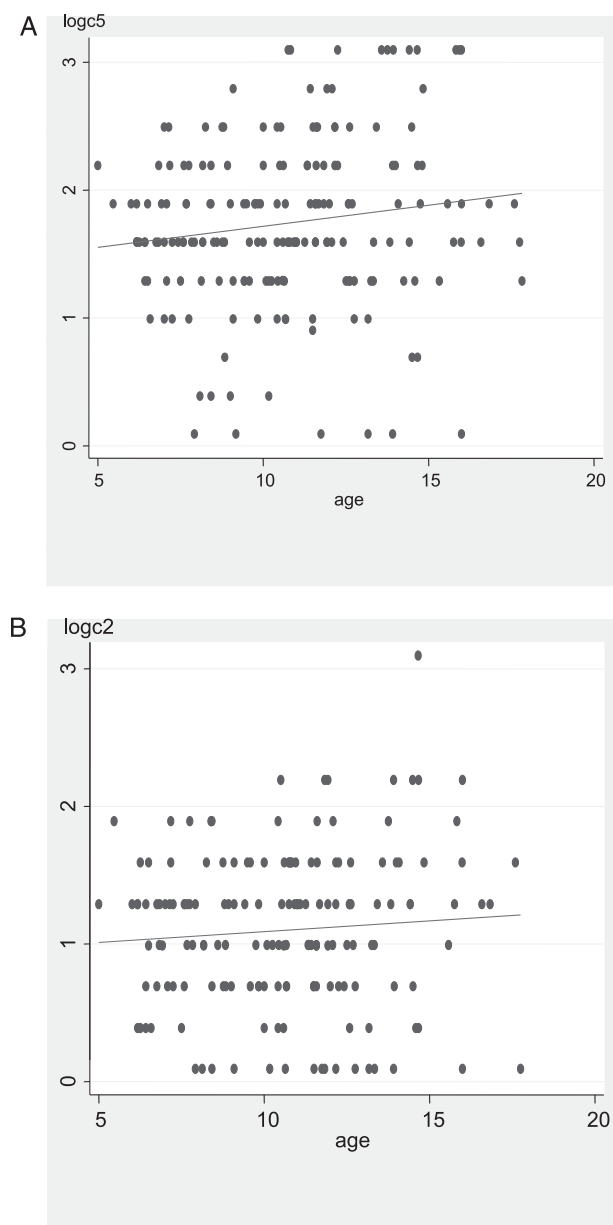


FIGURE 2. A, Scatter plot of log C5 vs age and regression line. The relationship between log C5 and age remained significant in multivariate analysis (see Table 2). B, Scatter plot of log C2 vs age and regression line. The relationship between log C2 and age remained significant in multivariate analysis (see Table 2). C2 = concentration of capsaicin required to stimulate two or more coughs; C5 = concentration of capsaicin required to stimulate five or more coughs.

These findings are consistent with various clinical cohorts that show similar proportions of boys to girls.^{3,35} In contrast, adult cohorts consistently show that women outnumber men by a ratio of ~2:1.³⁶ Although health-seeking behavior may influence the preponderance of women to men in adult cohorts, others have shown that it is more likely reflective of the pathophysiology because women have significantly higher CRS.^{9,11} Thus, our findings provide further objective evidence and confirm clinical studies and

publications that advocate that “children are not little adults” and that child-specific outcomes should be used in the clinical setting as well as in research for studies on cough. Clinicians accustomed to looking after children usually discriminate what is advocated in published studies, some of which include a discussion on children, but the recommendations (eg, using 2 weeks of 30-mg/d oral corticosteroids³⁷) are clearly inappropriate for the management of children with chronic cough. However, other clinicians do not discriminate and commonly extrapolate adult data to children, which sometimes result in delayed diagnosis of underlying lung disease³⁸ and substantial side effects, such as those from the inappropriate use corticosteroids for children with chronic cough.^{39,40}

Reasons for age influencing CRS can only be speculated. The most likely reason relates to the change in airways caliber with age that influences the distribution of intrapulmonary deposition of inhaled capsaicin. The smaller airways caliber in younger children (compared with older ones) likely results in more distal capsaicin distribution, as a constant flow was used in the cough challenge.²⁵ Cough receptors are not equally distributed, and distal airways are more sensitive to chemical stimuli.⁴¹

The present study is limited by the opportunistic use of data (ie, the cohort was not specifically enrolled to study these relationships). Thus, children enrolled in the asthma exacerbation study²⁴ did not have objective cough counts performed. Additionally, our cohort of children with chronic cough ($n = 77$) was smaller than that of Kelsall et al¹⁰ ($n = 86$ with objective cough counts performed). Thus, a type 2 error is possible, although unlikely, when considering the consistency of data described herein. Further, we did not include a cough-specific QOL questionnaire until recently, as none suitable for pediatrics was available.^{6,27} Further, the very low R^2 values for C2 and C5 (as independent factors) indicate that the relation is unlikely linear and the presence of other yet-to-be-defined influencing factors. However, the present study did not aim to determine all the factors influencing CRS measures but to specifically explore the influence of atopy and sex on cough outcome measures.

Despite of these limitations, the present study shows that atopy does not influence important cough outcome measures in children with and without chronic cough. However, age but not sex influences cough sensitivity in children. Older children have higher CRS values (ie, less sensitive to capsaicin) than younger children. Unlike adult data, sex does not affect objective cough counts or VAS score, a validated parent-proxy subjective cough score. For studies on cough in children, it is essential that subjects and control subjects be age matched, but atopic status and sex are likely less important.

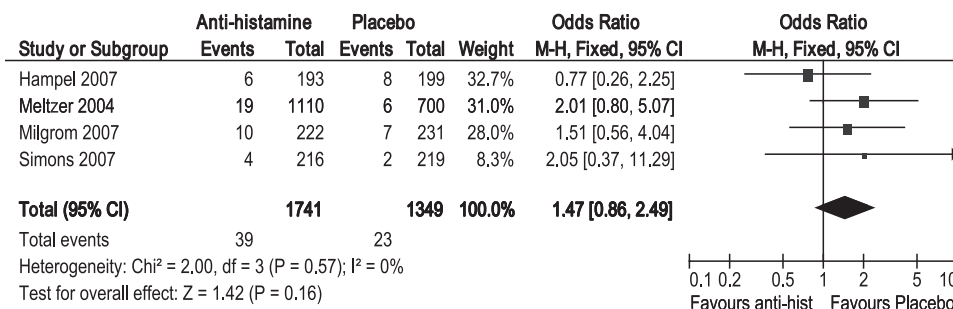


FIGURE 3. Forest plot from a Cochrane review of safety-based studies on second-generation antihistamines in children with allergic rhinitis. The Forest plot shows that children randomized to the active arm had a nonsignificant increased risk of developing cough (OR, 1.47; 95% CI, 0.86-2.49). anti-hist = antihistamine; df = degrees of freedom; M-H = Mantel-Haenszel test. (Reprinted from Chang et al.³⁴)

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Author contributions: Dr Chang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Chang: contributed to the conception of the study, performed the data analysis, and drafted the manuscript.

Dr Gibson: contributed to the included studies and reviewed and contributed to the final manuscript.

Ms Willis: contributed to combining the data from the various cohorts and reviewed and contributed to the final manuscript.

Ms Petsky: contributed to the data collection for children in the study evaluating the relationship between cough and exercise and reviewed and contributed to the final manuscript.

Dr Widdicombe: contributed to the included studies and reviewed and contributed to the final manuscript.

Dr Masters: contributed to the included studies and reviewed and contributed to the final manuscript.

Dr Robertson: contributed to the included studies and reviewed and contributed to the final manuscript.

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Additional information: The e-Figures can be found in the Online Supplement at <http://chestjournal.chestpubs.org/content/140/2/324/suppl/DC1>.

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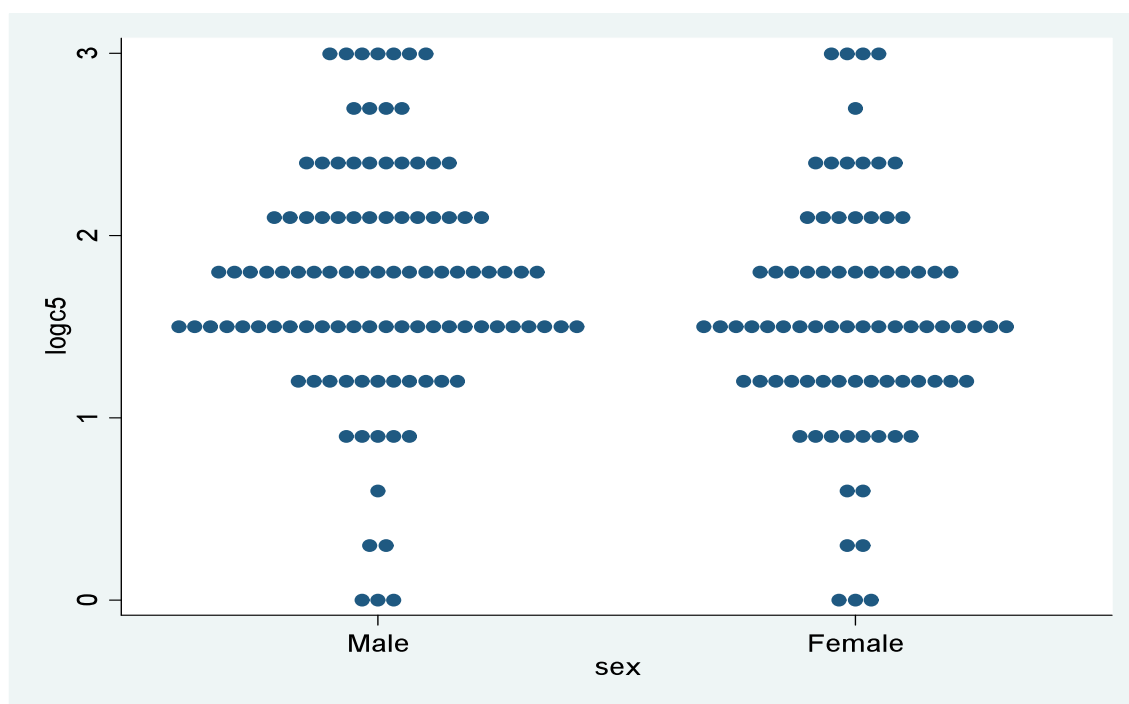
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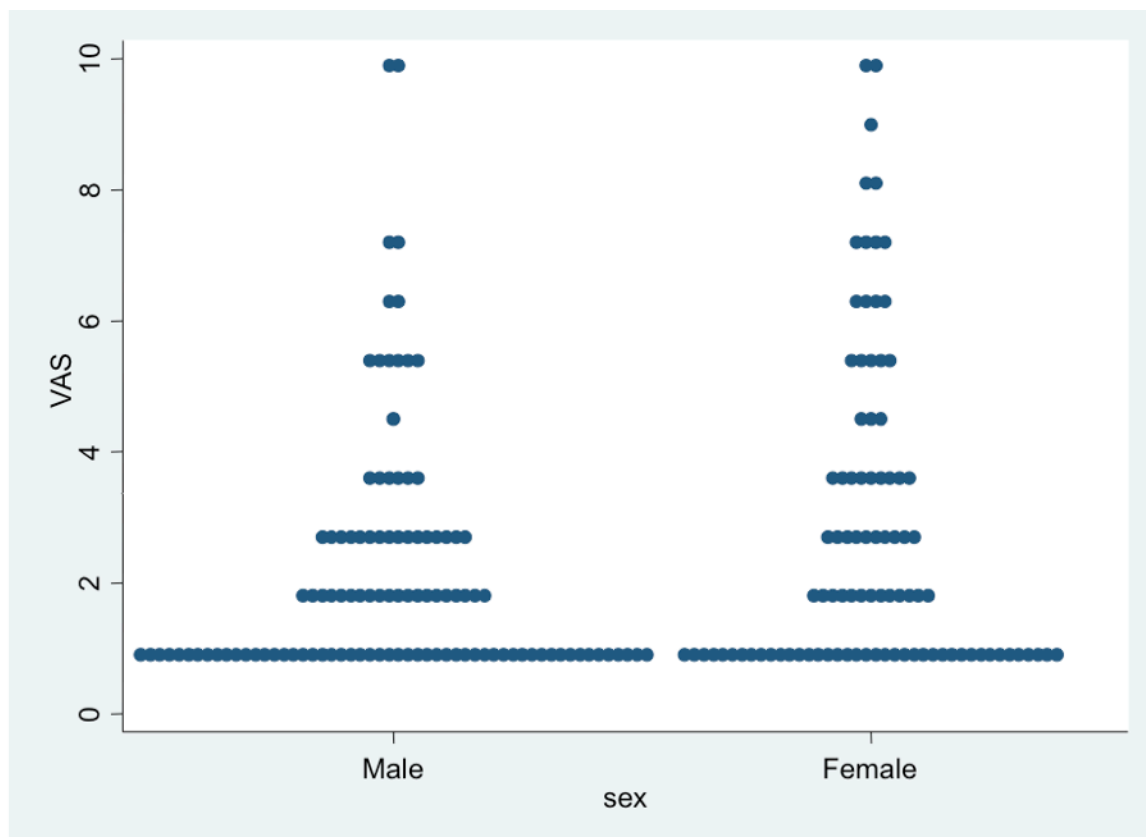
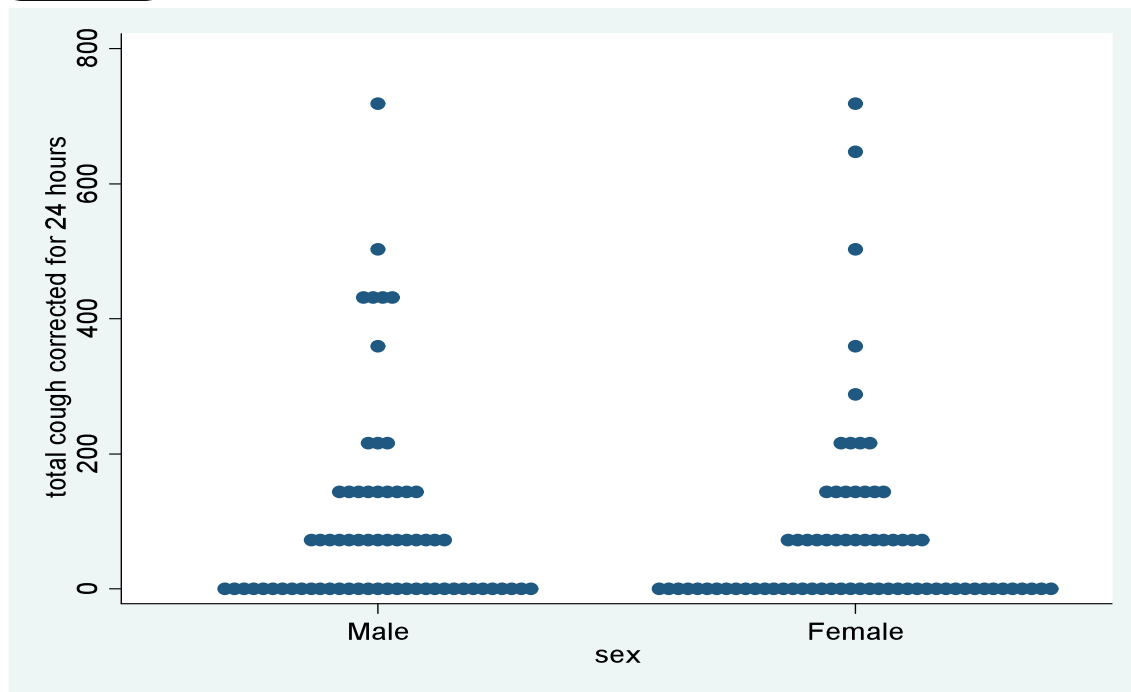
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e-Figure 1. Scatter plot of cough outcomes (C5, objective cough counts and VAS score) in children grouped by gender



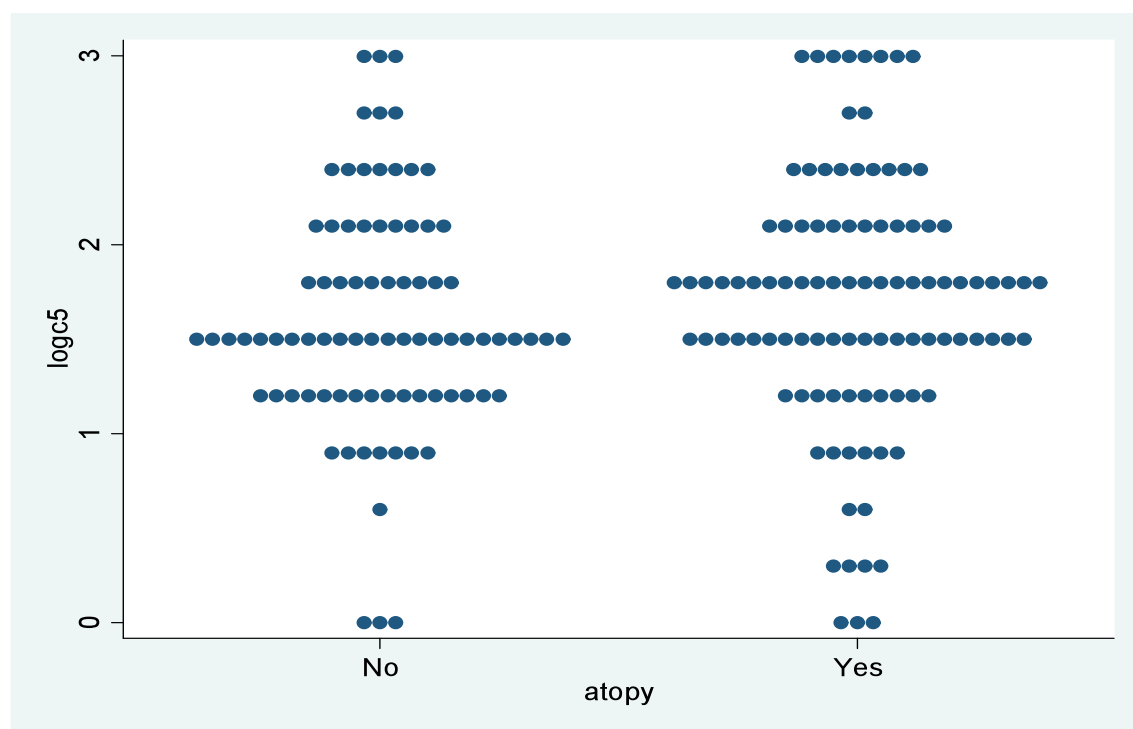
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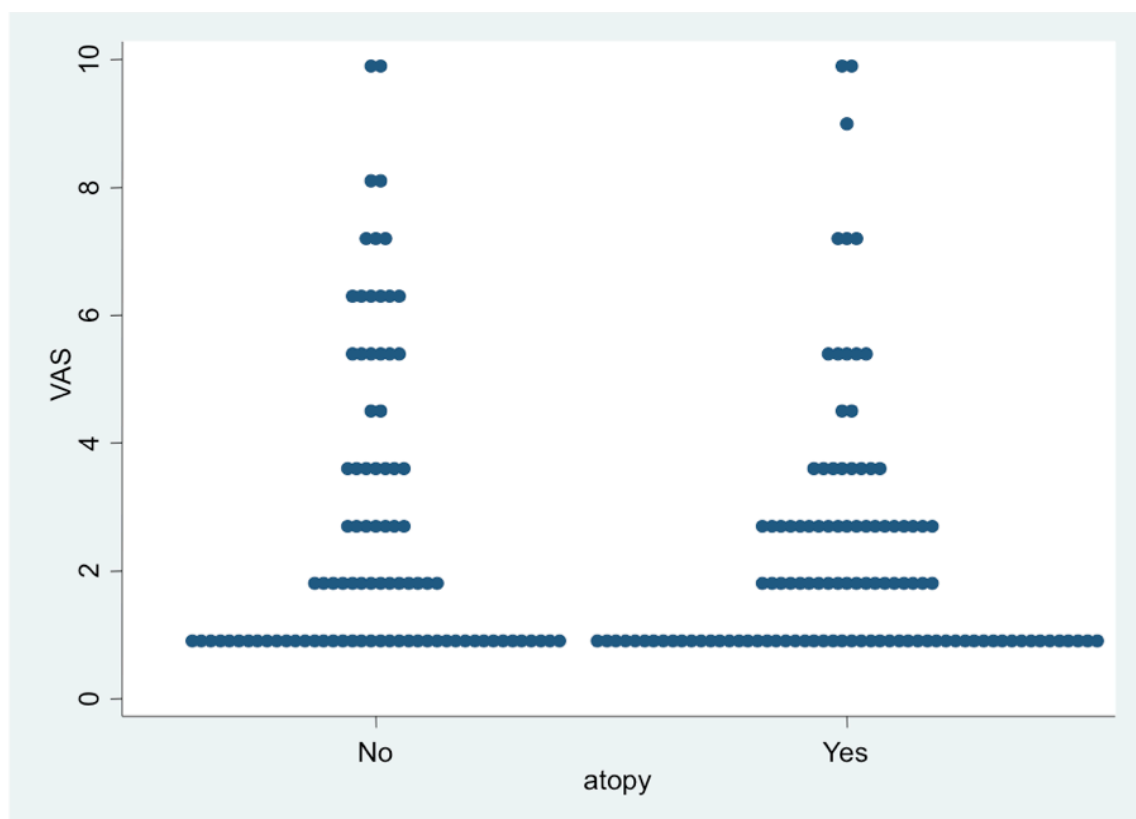
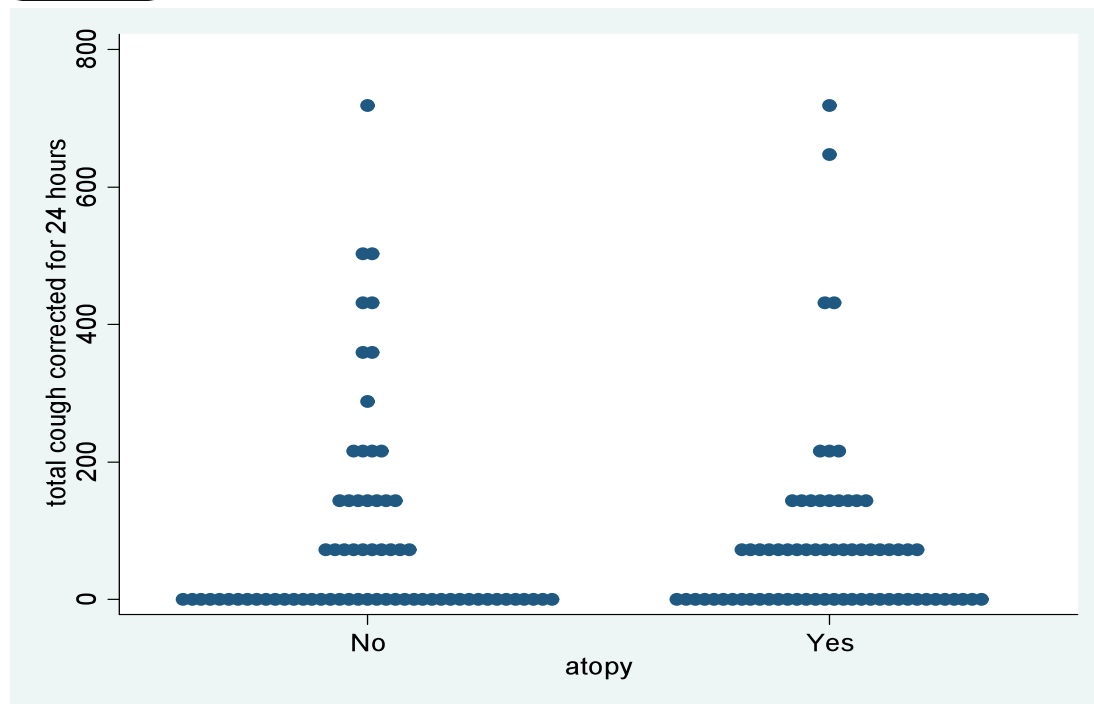
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e-Figure 2. Scatter plot of cough outcomes (C5, objective cough counts and VAS score) in children grouped by atopy



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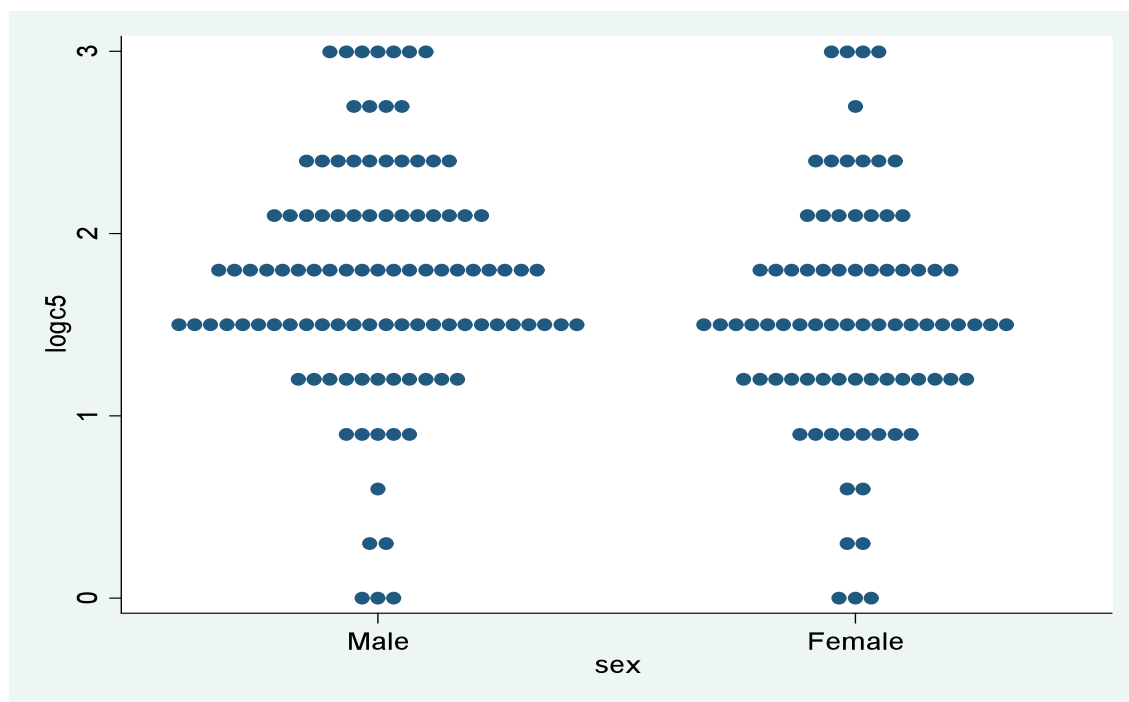




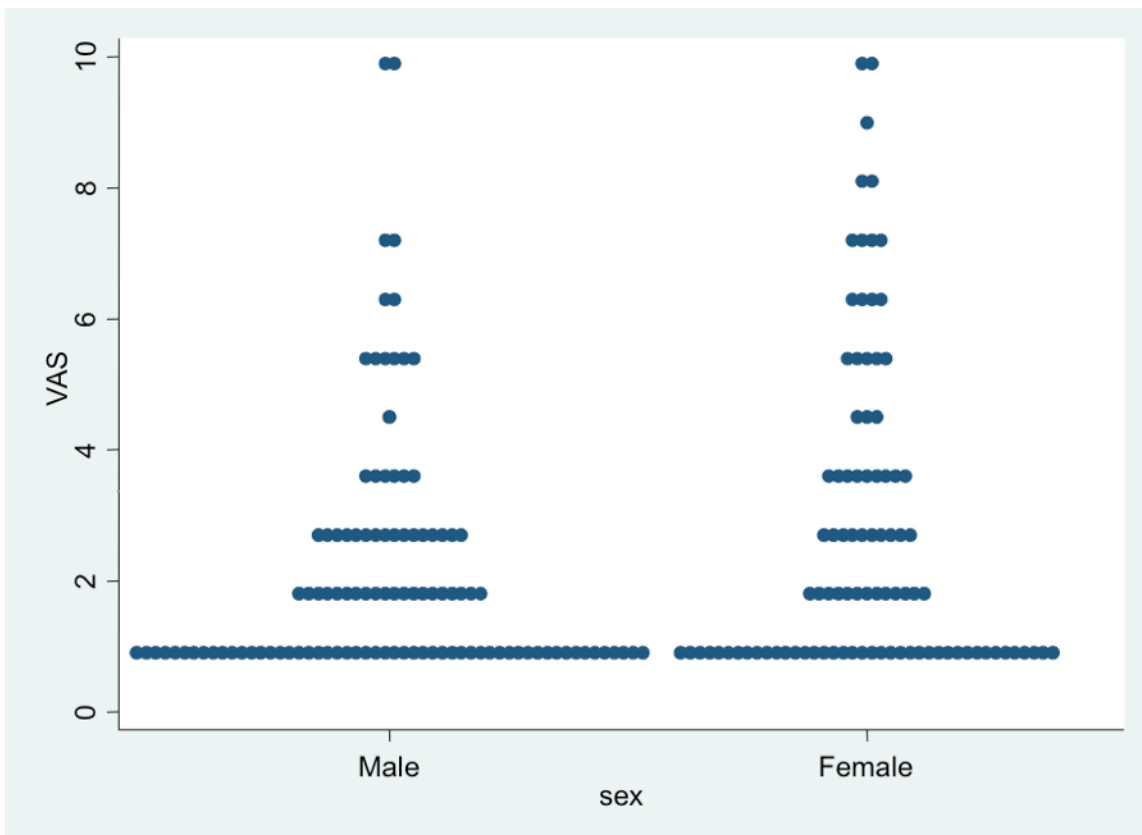
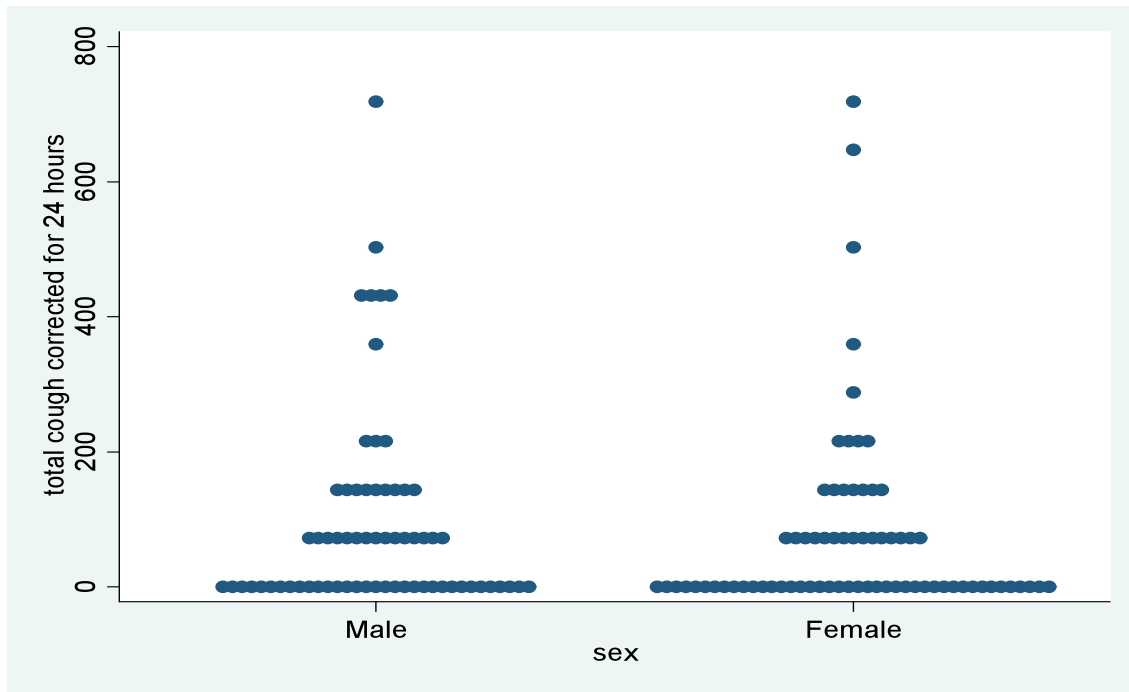
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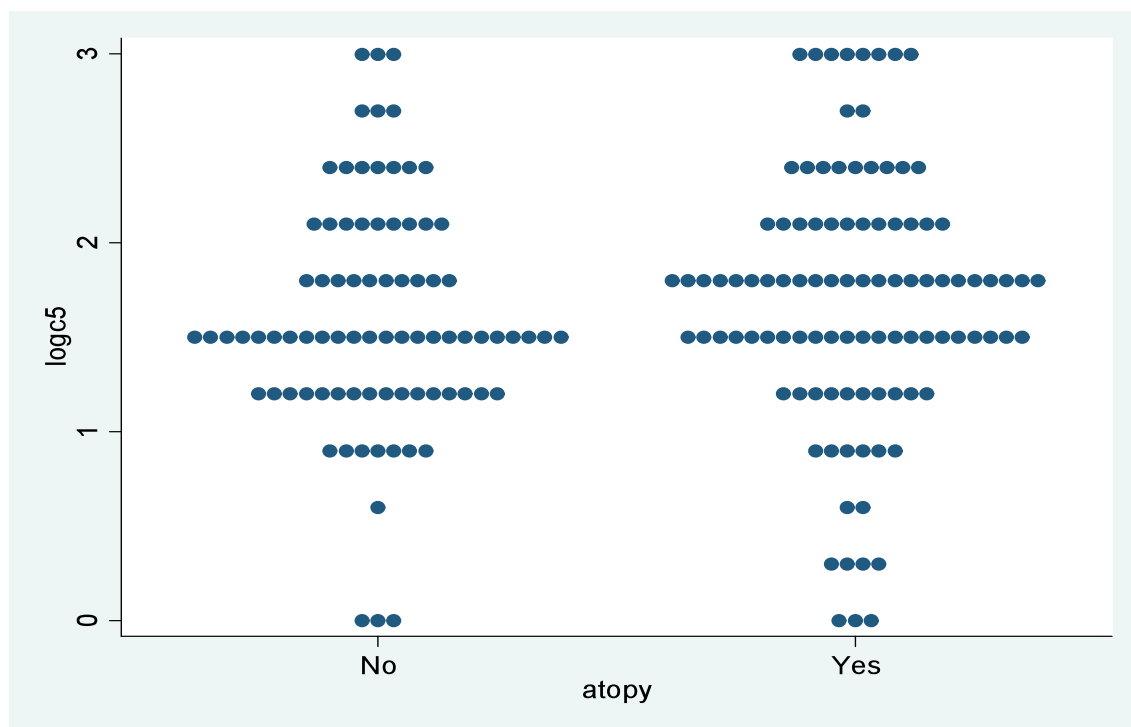
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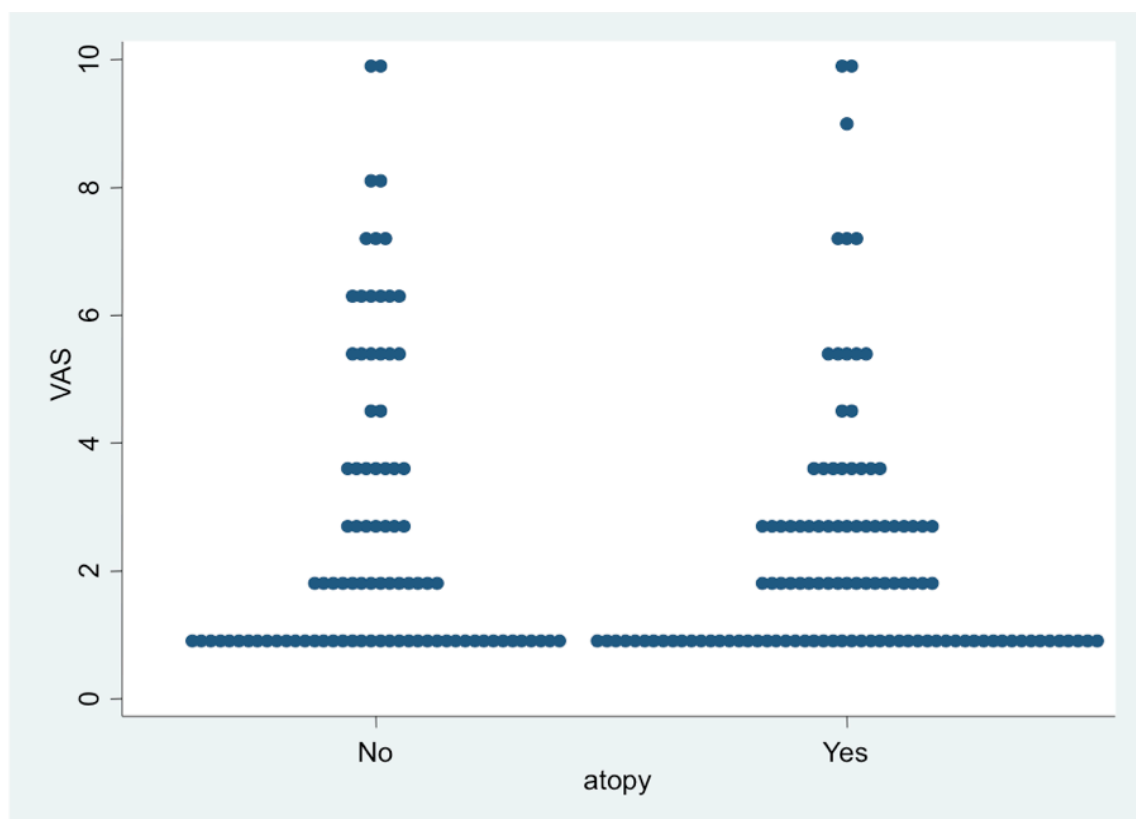
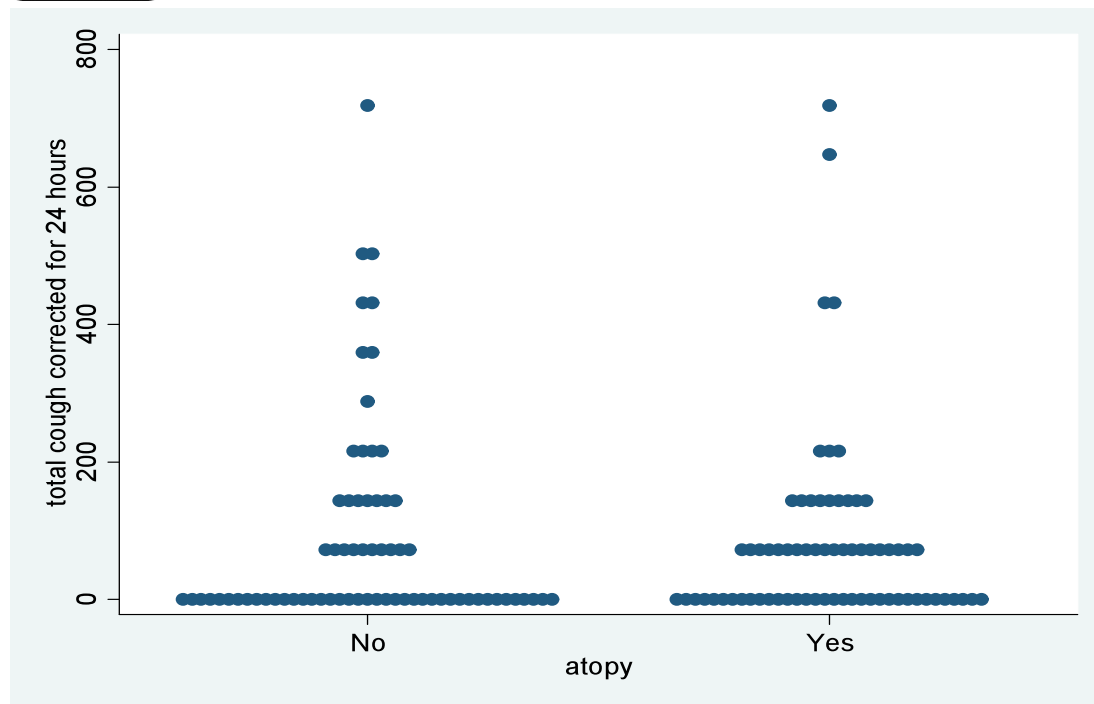
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