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Early life chronic inflammatory conditions predict low back pain in adolescence and young adulthood

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Original article

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Significance

Low back pain (LBP) is a prominent and significant health problem and associations between inflammatory conditions and LBP have been found frequently in older populations. We found that children with respiratory or atopic conditions and those with several chronic inflammatory conditions are at increased odds of impactful LBP in adolescence and young adulthood. In clinical practice and future research there is a need to consider comorbidities also in younger populations.

Abstract:

Background: Associations between inflammatory conditions and low back pain (LBP) have been found frequently in older populations. However, the nature of these relationships in younger populations is unknown. This study aimed to investigate associations between early life chronic or recurrent inflammatory conditions and impactful LBP in adolescence and young adulthood.

Methods: In this longitudinal study we used data from the Raine Study Gen2 participants at the 1,2,3,5,8,10,14,17,20, and 22-year follow-ups (N=2868). Data were collected on

inflammatory conditions from one to 22-years of age and occurrences of impactful LBP from 14 to 22-years of age. Longitudinal and cross-sectional associations between inflammatory conditions and impactful LBP occurrence were examined. Potential dose response relationships between the number of inflammatory conditions and impactful LBP were also assessed. Logistic regression models were used in the analysis.

Results: Participants with respiratory or atopic conditions during childhood had increased odds of future impactful LBP in adolescence and young adulthood (odds ratio(OR)[95% confidence interval (CI)] = 1.29[1.07, 1.54], 1.23[1.02, 1.49] respectively). There were cross-sectional associations between inflammatory conditions including respiratory, skin, musculoskeletal, autoimmune, and atopic conditions, with impactful LBP. Participants with two illnesses and three or more illnesses had an increased odds (OR[95% CI] = 1.68[1.30, 2.18]) and (OR[95% CI] = 2.12[1.54, 2.89]) respectively of reporting impactful LBP.

Conclusions: Overall, longitudinal and cross-sectional associations of respiratory and atopic conditions with impactful LBP in adolescence and young adulthood were identified. More evidence is needed to determine if there is a causal relationship between chronic inflammatory conditions and impactful LBP.

Introduction

Low back pain (LBP) is a prominent and significant health problem. From early adolescence, LBP is ranked within the top ten causes of years lived with disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). The LBP prevalence increases in adulthood when it becomes the leading cause of years lived with disability globally (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Low back pain in adolescence is linked with LBP in adulthood (Hestbaek et al., 2006a). Many other chronic or recurrent inflammatory conditions commonly commence during childhood including respiratory disease, endocrine disorders, and digestive system disorders. In addition, adults with both respiratory and digestive disorders have an increased prevalence of LBP compared to adults without respiratory and digestive disorders (Holmberg et al., 2005).

There are a couple potential mechanisms in which inflammatory conditions could be associated with LBP. If we consider a temporal relationship, an inflammation-associated activation of the hypothalamic-pituitary-adrenal axis is a plausible biological link between chronic or recurrent inflammatory conditions and LBP (Hurwitz and Morgenstern, 1999).

Early inflammatory conditions may alter hypothalamic-pituitary-adrenal axis function through direct action or via epigenetics (Polli et al., 2019; Shanmugam and Sethi, 2013), facilitating further mechanical or psychosocial stressors and overall hypersensitivity and pain. Early life is a critical period of development, and early life stresses can influence future nociceptive processing (Waller et al., 2020). These associations have been found previously between early-life psychological stresses and increased incidence of chronic pain in later life (Burke et al., 2017), as well as between early-life pain experiences and spinal pain in pre-adolescence (Joergensen et al., 2019).

Alternately another potential mechanism may be that, co-morbid inflammatory conditions and LBP could have a shared/common origin (Holmberg et al., 2005). A significant proportion of LBP itself could be an inflammatory condition. Hypothetically, the inflammatory conditions as well as LBP could therefore occur at any time during the lifetime and share a common cause.

Associations between chronic or recurrent inflammatory conditions and LBP have been found frequently in older populations (Heliövaara et al., 1991; Holmberg et al., 2005; Smith et al., 2009). However, the nature of these relationships in younger populations is unknown. Therefore, the overall aim of this study was to investigate for associations between early life chronic or recurrent inflammatory conditions with LBP in adolescence and young adulthood.

The specific objectives were 1) to investigate the longitudinal association between inflammatory conditions in childhood and impactful LBP occurrence from adolescence to young adulthood, 2) to investigate the cross-sectional association between inflammatory conditions from adolescence to young adulthood and impactful LBP occurrence, and 3) to investigate potential dose response relationships between the number of chronic inflammatory conditions and the occurrence of impactful LBP.

Methods

Study Design and Ethics Permissions

Data was used from the Raine Study Gen2 participants at the 1, 2, 3, 5, 8, 10, 14, 17, 20, and 22 year follow ups. The Raine Study commenced as a Western Australian Pregnancy Cohort, with mothers recruited between May 1989 and Nov 1991 at King Edward Memorial Hospital

for Women. There were 2868 children recruited into the Raine Study Cohort. The children (Gen2) have been assessed at regular timepoints from birth, until present (27 years) (McKnight et al., 2012; Straker et al., 2017). The cohort at inception was predominantly Caucasian (93%).

All aspects of the Raine Study were approved by the Human Ethics Committees at King Edward Memorial Hospital, Princess Margaret Hospital, University of Western Australia and/or Curtin University. The adolescents/young adults and/or their parents or guardian provided written informed consent for data collection. Ethics approval for the current study was approved by Murdoch University Human Research Ethics Committee (Approval number: 2018/226).

Exposure Variables: Chronic or recurrent inflammatory conditions

Information on chronic inflammatory conditions was obtained at age; 1, 2, 3, 5, 8, 10, 14, 17, 20, and 22 years regarding any self-reported diagnosed conditions (by parents in early years and participants in later years) and, where possible, verified through medical records, medication use, hospital admissions, as well as ICD-9 codes. We included chronic or recurrent inflammatory conditions. Exclusion criteria included: neoplasms, blood conditions if not autoimmune or atopic, acute conditions or if unknown if acute or chronic, mental and neurological conditions caused by birth trauma or congenital defects, or if it was unknown to be an inflammatory condition due to insufficient information (e.g. hypothyroidism with unknown cause).

Firstly, we categorised chronic inflammatory conditions using ICD-9 categories including: 1. endocrine system, 2. respiratory system, 3. digestive system, 4. skin and subcutaneous tissues (including the eye), and 5. musculoskeletal system and connective tissues. Secondly, additional categories (not mutually exclusive to the first five categories) included autoimmune and atopic conditions. These categories were utilised to determine exposures to chronic inflammatory conditions within specific systems (e.g., endocrine, respiratory), as well as inflammatory conditions of the same type (e.g., autoimmune, atopic). Thirdly, all chronic inflammatory illnesses were included together in a final exposure category of 'any inflammatory condition'. The Appendix shows each of the exposure categories.

For objective one, we included inflammatory conditions from 1 to 10 years of age to capture inflammatory conditions in childhood that were likely to precede the onset of back pain (Smith et al., 2017). For objective two, inflammatory conditions from 14 to 22 years were included to investigate the cross-sectional association between inflammatory conditions and LBP from adolescence to young adulthood. For objective three, we included inflammatory conditions from 1 to 22 years, as this considers inflammatory conditions at any point from childhood to young adulthood. Participants were considered to have a condition if they reported they were diagnosed having that condition at least once within the respective timeframe i.e. for objective one (1-10 years).

Low back pain outcomes

The occurrence of LBP was assessed at 14, 17, 20, and 22 years of age. Participants self-reported LBP occurrences within the last month, including the impact of LBP on care-seeking and activity participation. At each time point, participants answered five questions: “Has your low back been painful at any time in the last month?”, “Have you missed work or school due to low back pain?”, “Has low back pain interfered with your normal activities?”, “Has low back pain interfered with recreational physical activities?”, “Have you sought professional advice or treatment for low back pain?”, “Have you taken medication to relieve low back pain?” At the 14-year follow-up questions were asked about any “back pain” rather than specifically “low back pain”.

The outcome variable of low back pain for our analysis was ‘impactful LBP’, which we defined as having LBP plus answering affirmatively to at least one of the LBP impact questions (i.e., questions 2 – 5) (Coenen et al., 2017) at least once at 14, 17, 20, or 22 years of age. Merely having back pain in adolescence may be a normal life experience and potentially of benign nature with no long-term problems (Burton et al., 1996). Impactful LBP was used as the outcome variable of LBP in an attempt to exclude trivial occurrences of LBP.

Potential confounders

Potential confounders included sex, body mass index, and pubertal status. The trend in the literature shows a higher prevalence of back pain with advancing age, more advanced pubertal status, and female sex (Beynon et al., 2019a; Beynon et al., 2019b). There are

mixed results in the literature regarding the relationship between body mass index and back pain (Beynon et al., 2019a; Beynon et al., 2019b).

Pubertal status was assessed at 14 and 17 years of age using the Tanner stages (Tanner, 1962). Tanner stages were reported on a scale of 1 to 5, with higher scores representing later pubertal status, based on self-assessments of pubic hair development in boys and breast development in girls (Marshall and Tanner, 1969, 1970). Height was measured with a Holtain Stadiometer (nearest .1 cm); body weight was measured using a Wedderburn Chair Scale (nearest 100g). Body mass index was calculated by taking weight(kg)/height(m)^2. Age and sex specific body mass index categories for normal weight, overweight, and obesity were calculated for all participants (Vidmar et al., 2013).

Statistical analysis

Demographic data were reported descriptively. We conducted analyses to determine the associations between chronic or recurrent inflammatory conditions and impactful LBP, using univariate and adjusted logistic regression models with robust standard errors. Covariates were introduced into the model and kept within the model if it was associated with back pain, or if it made significant changes to the association between the exposure variable and back pain. For each exposure variable a minimum of 10 cases (people with the condition of interest) were needed in order to run the model. The effects of risk factors were summarised using odds ratios (OR) with 95% confidence intervals [95% CI] and *p* values. Data were analysed using Stata S/E version 15 (StataCorp, TX).

Results

The demographic characteristics of participants at each follow up are presented in Table 1. From the ages of 14 to 22 years 1152 participants (59%) reported at least one episode of impactful LBP. Pubertal status and body mass index were not univariately associated with LBP and therefore not included in the models. Sex was found to be a significant covariate therefore all models are adjusted for sex.

Objective 1: Longitudinal association between inflammatory conditions in childhood and impactful low back pain occurrence from adolescence to young adulthood

Fig. 1 demonstrates the relationship between participants with chronic or recurrent inflammatory conditions from one to ten years of age and subsequently whether impactful LBP manifests in adolescence or young adulthood. There were only 8 and 5 participants with endocrine and musculoskeletal conditions (1 to 10 years of age) respectively therefore these models could not be created. The odds ratios with 95% confidence intervals to develop future LBP for participants with respiratory conditions, atopic conditions, and any inflammatory condition, respectively were (1.29 [1.07, 1.54]), (1.23 [1.02, 1.49]), and (1.25 [1.03, 1.52]). No associations were found between digestive, skin, or autoimmune conditions and LBP (Fig. 1).

Objective 2: Cross-sectional associations between inflammatory conditions and impactful low back pain occurrence from adolescence to young adulthood.

Participants with respiratory, skin, musculoskeletal, autoimmune, or atopic conditions at 14 to 22 years of age had an increased odds of impactful LBP (Fig. 2). Further, participants with any inflammatory condition compared to those with no inflammatory condition had increased odds of LBP (OR [95% CI]= 1.45 [1.20, 1.76]). There was no association found between endocrine and digestive conditions, and LBP (Fig. 2).

Objective 3: Dose-response relationship between number of chronic inflammatory conditions and impactful low back pain

Participants with a greater number of chronic inflammatory conditions from 1 to 22 years had increased odds of impactful LBP at 14 to 22 years (Fig. 3). Participants with two illnesses and three or more illnesses had an increased odds (OR [95% CI] = 1.68 [1.30, 2.18]) and (OR [95% CI] = 2.12 [1.54, 2.89]) respectively of reporting LBP (Fig. 3). The increased odds ratios demonstrate evidence of a potential dose-response relationship.

Discussion

In longitudinal analysis, participants with respiratory or atopic conditions during childhood had increased odds of future impactful LBP in adolescence/young adulthood. However, there were no associations found between digestive, skin, or autoimmune conditions during childhood and LBP in adolescence and young adulthood (objective 1). There were cross-sectional associations between chronic inflammatory conditions including respiratory, skin,

musculoskeletal, autoimmune, and atopic conditions, and LBP in adolescence to young adulthood (objective 2). Participants with a greater number of chronic inflammatory conditions had increased odds of LBP in adolescence and young adulthood (objective 3). Use of the Raine Study data has enabled a comprehensive look at comorbidity of chronic inflammatory conditions and impactful LBP over a long period of time.

Potential mechanisms

Within objective one we investigated whether there was a temporal relationship between early inflammatory conditions and later impactful LBP, in children not reporting LBP at the time of having reported other inflammatory conditions. Such a finding could support the theory that early life inflammation, of any type of inflammatory condition, could explain why LBP is likely to occur through a change of the hypothalamic-pituitary-adrenal axis (Hurwitz and Morgenstern, 1999; Polli et al., 2019; Shanmugam and Sethi, 2013).

Within objective two we investigated the cross-sectional association between inflammatory conditions and LBP. Such comorbidity could indicate a shared underlying (inflammatory) mechanism for both the comorbidity and LBP, thus indicating that LBP would be an inflammatory condition. Association between inflammatory conditions and impactful LBP were more consistent in the cross-sectional analysis than in the longitudinal analysis, suggesting that when the inflammatory condition is active LBP may be yet another of its manifestations.

We cannot infer causation based on these analyses but rather consider whether chronic inflammatory conditions could predict LBP in adolescence and young adulthood. The association between respiratory conditions and LBP is consistent with the broader literature. Cross-sectional studies have shown that adults with breathing difficulties (Smith et al., 2006), respiratory diseases including asthma (Heliövaara et al., 1991; Hurwitz and Morgenstern, 1999; Wright et al., 1995), or allergies (Hurwitz and Morgenstern, 1999) had higher odds of having back pain compared to those without the condition. Additionally, asthma in adolescence has been found to be associated with future LBP (Hestbaek et al., 2006b). Our analysis supports these findings and expands them using both cross-sectional and longitudinal analyses.

In considering temporality we considered childhood chronic illnesses diagnosed in early childhood in LBP free individuals and subsequently whether LBP manifests in adolescence or young adulthood (objective 1). Back pain with impact generally does not originate until around pubertal or after puberty. In considering this longitudinal association only respiratory or atopic conditions had increased odds of future LBP.

The dose response relationship was examined in objective three. Participants with a greater number of chronic inflammatory conditions had increased odds of LBP in adolescence and young adulthood. This dose-response relationship has also been consistently seen within the previous literature. Adults with both respiratory and digestive (Holmberg et al., 2005), or respiratory and gastrointestinal disorders (Smith et al., 2009) had an increased risk of developing back pain as compared to those without the conditions.

More evidence is needed to elucidate if there is a causal relationship, but there is an association between some chronic inflammatory conditions and LBP. The associations found in this study suggests further investigations related to causality are a reasonable thing to do.

Research and clinical implications

The results from this study show the need to consider co-morbidities in clinical practice and future research. Clinicians and researchers tend to work in clinical silos. Musculoskeletal clinicians and researchers should consider other conditions that are potentially having a role in the musculoskeletal complaint. Musculoskeletal clinicians may ask about past and current medical history, but they should also consider this medical history within the treatment plan potentially through interprofessional collaborations.

Low back pain is known to be complex and multifactorial (Hartvigsen et al., 2018). For example in the Raine Study participants, exposure to pain, physical factors, psychological factors, social factors and lifestyle factors at 14 years of age have been shown to be associated with the reporting of LBP at 17 (Smith et al., 2017). The results should be interpreted within the broader understanding of LBP as a complex disorder.

Strengths and limitations

The population is a community dwelling sample, rather than just a clinical population which increases the external validity. Merely having back pain in adolescence may be a normal life

experience and potentially of benign nature with no long-term problems (Burton et al., 1996). Impactful LBP was considered in this study. This definition captures the population that could be associated with an increasing health and societal burden from LBP.

At 14 years of age questions were asked about back pain rather than specifically LBP. Back pain covers a bigger part of the spine potentially leading to a larger prevalence estimate at the 14-year timepoint. Additionally, the severity and duration of LBP were unknown. In considering inflammatory conditions during childhood, certain conditions had a low prevalence. For example, there were only thirty participants diagnosed with chronic autoimmune inflammatory conditions from one to ten years of age. Compared with 1391 participants diagnosed with chronic respiratory inflammatory conditions from one to ten years of age. The low prevalence of certain conditions could lead to a type two error, failing to reject the null hypothesis. For objective one, we included inflammatory conditions from 1 to 10 years of age to capture inflammatory conditions in childhood that were likely to precede the onset of back pain. However, it is possible that different, or stronger, results might be found if a longer period of childhood was considered. Additionally, the chronic inflammatory conditions were self-reported and, where possible, verified through medical records. No information was included on the duration of the condition, age at the time of diagnosis, or severity of conditions. Therefore, there could have been a difference between participants with the same diagnosis as well as under- or over-diagnosis based on self-reported data. While we did attempt to control for confounding by including covariates in our models, we were unable to account for every possible source of confounding. Therefore, there is a potential for residual confounding.

Conclusion

Overall, longitudinal and cross-sectional associations of respiratory and atopic conditions, with impactful LBP in adolescence and young adulthood were identified. More evidence is needed to determine if there is a causal relationship between chronic inflammatory conditions and impactful LBP, or if there is a common origin for these conditions.

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Authors Contributions

AB, JH, CLY, DB and BW were involved with the concept and design. Statistical analysis was performed by AB, JH and AJ. All authors were involved with interpretation of the results and drafting the manuscript. All authors reviewed and approved the final manuscript.

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Legends

Tables

Table 1: Number of participants with data

Figures

Fig. 1: Longitudinal association between chronic inflammatory conditions from 1 to 10 years and impactful low back pain occurrences 14 to 22 years.

Abbreviations: N: number of participants with the condition, OR: odds ratio, 95% CI: 95% confidence intervals, Any: any inflammatory condition. Note: All models adjusted for sex.

Fig. 2: Cross-sectional association between inflammatory conditions and low back pain occurrences from 14 to 22 years.

438 *Abbreviations: N: number of participants with the condition, OR: odds ratio, 95% CI: 95%*
439 *confidence intervals, Any: any inflammatory condition. Note: All models adjusted for sex.*

440

441 **Fig. 3:** Dose response relationship between number of chronic inflammatory conditions and
442 impactful low back pain.
443 *Abbreviations: N: number of participants with the condition/s, OR: odds ratio, 95% CI: 95%*
444 *confidence intervals. Note: All models adjusted for sex.*

Appendix:

Exposure categories of chronic or recurrent inflammatory conditions with included conditions (conditions reported by participants).

1. Endocrine system:
   - Diabetes mellitus type 1
   - Addison's disease
   - Hashimoto's disease
   - Autoimmune lymphoproliferative syndrome
2. Respiratory system:
   - Chronic or allergic rhinitis
   - Chronic sinusitis
   - Chronic tonsillitis
   - Simple chronic bronchitis
   - Bronchiectasis
   - Asthma
3. Digestive system:
   - Oesophageal reflux
   - Gastritis
   - Crohn's disease
   - Eosinophilic gastroenteritis
   - Chronic pancreatitis
   - Celiac disease
4. Skin and subcutaneous tissues (including the eye):
   - Atopic dermatitis
   - Psoriasis
   - Chronic conjunctivitis
   - Eczematous dermatitis- eyelid
5. Musculoskeletal system and connective tissues:
   - Systemic lupus erythematosus
   - Juvenile rheumatoid arthritis
   - Ankylosing spondylitis
   - Polymyalgia rheumatica
6. Autoimmune conditions:
   - Diabetes mellitus type 1
   - Addison's disease
   - Hashimoto's disease
   - Autoimmune lymphoproliferative syndrome
   - Immune thrombocytopenic purpura
   - Wegener's granulomatosis
   - Celiac disease
   - Psoriatic arthropathy
   - Psoriasis
   - Systemic lupus erythematosus
   - Juvenile rheumatoid arthritis
   - Ankylosing spondylitis
7. Atopic conditions:

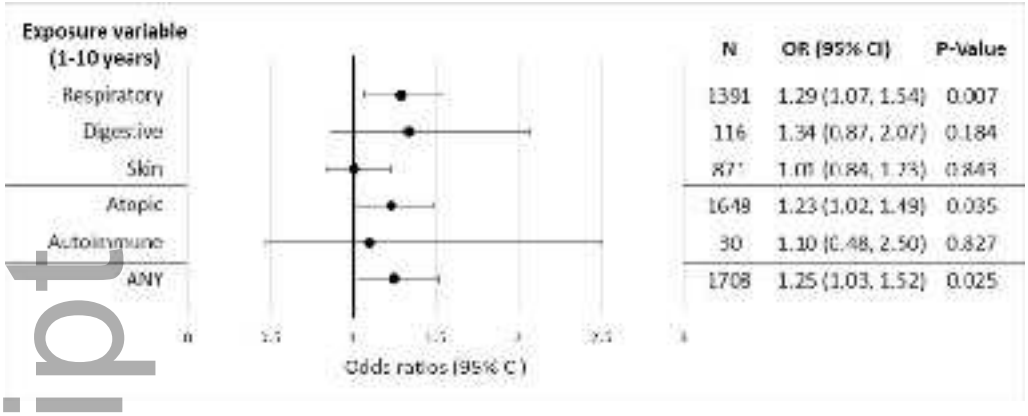
- Atopic dermatitis
- Chronic conjunctivitis
- Eczematous dermatitis- eyelid
- Chronic or allergic rhinitis
- Asthma

8. Any:
    - Includes any of the above conditions

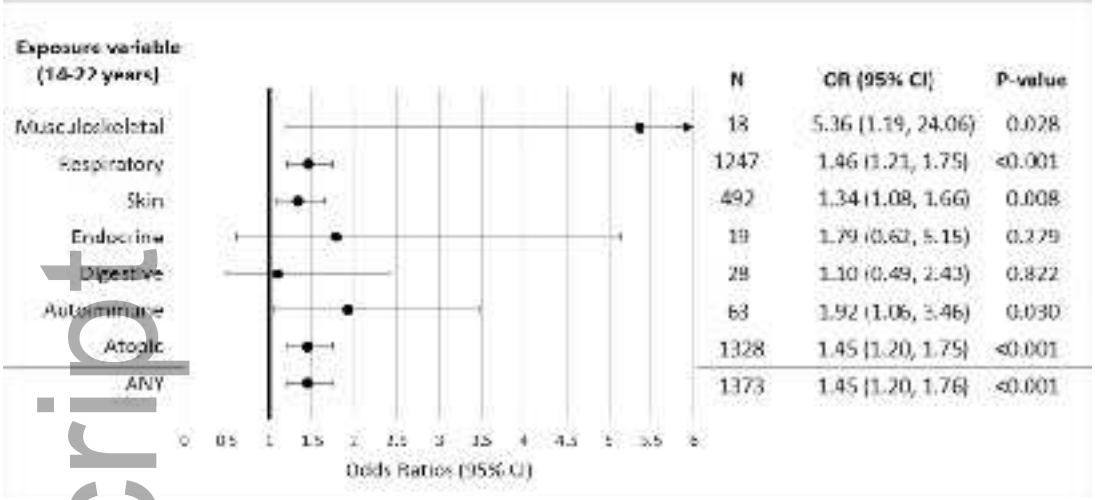
Table 1: Number of participants with data

Follow-up	Total participants: n	Age (years): mean (SD)	Female: n (%)
1	2430	1.2 (0.1)	1193 (49.1)
2	1974	2.1 (0.1)	945 (47.9)
3	2260	3.1 (0.1)	1110 (49.1)
5	2236	5.9 (0.2)	1082 (48.4)
8	2142	8.1 (0.3)	1042 (48.6)
10	2048	10.6 (9.8)	989 (48.3)
14	1865	14.1 (0.2)	906 (48.6)
17	1693	17.1 (0.3)	849 (50.2)
20	1577	20.0 (0.5)	787 (49.9)
22	1235	22.2 (0.8)	640 (51.8)

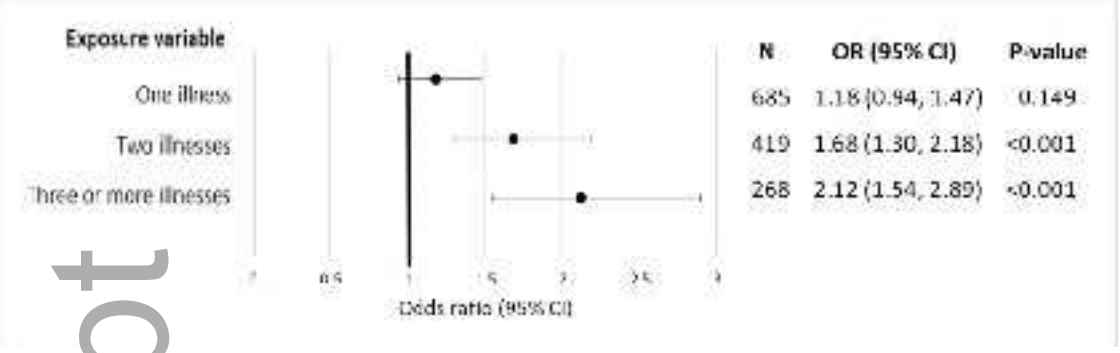
SD: standard deviation



ejp_1700_f1.jpg



ejp_1700_f2.jpg



ejp_1700_f3.jpg