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Academic Stress and Adolescent TB: From Latent Infection to Active Disease

Hanyu Yin

Faculty of Social Science and Public Policy, King's College London, London, UK
hanyuyin@kcl.ac.uk

Abstract. Tuberculosis (TB) is one of the significant infectious diseases that affect people of all age groups. Adolescents are at high risk due to the fact that their immune system is in the process of development and strong academic pressures are exerted on them. This review aims to examine the evidence and outbreak cases of the epidemiological question of whether academic stress can be considered an independent risk factor for progression from latent TB infection (LTBI) to active TB in adolescents. Epidemiological data reveal that TB risk increases with grade level, and the highest risk occurs for senior high school students, particularly during the national college entrance examination (UAN) in June. TB outbreaks in boarding schools are common, with high attack rates, due to the failure to diagnose, screen, or provide preventive treatment. Academic stress is related to examination pressure, a pile of homework, sleeplessness and social expectations. Chronic stress can trigger the HPA axis and ultimately cause an increase in glucocorticoids and immune imbalance and depression, which impair anti-TB immunity. A vicious cycle, as long treatment causes an adolescent patient to miss school and adds to the stress in their life. This paper indicates that academic stress could be a factor for TB in adolescents, in addition to poor nutrition and sleep deprivation. Going forward, mental health should be incorporated into TB control during stressful periods. There is a need for additional research to substantiate the causal pathway and to create effective interventions.

Keywords: Academic stress, adolescent, tuberculosis

1. Introduction

Tuberculosis (TB) is an infectious disease that affects all age groups. Adolescents are considered a high-priority sub-population since they are still in the process of their physiological development and are in a unique psychosocial setting that changes their susceptibility to disease from that of younger children. The risk of active TB is higher in adolescents than in children aged 5-10 years. The immune system is in a developmental dynamic transition during adolescence and is continually exposed to mycobacterial pathogens. The academic load, the frequent examinations, the strict campus control and the academic pressure result in a chronic psychosocial stress. Such stressors could result in the weakening of the host's immune defence, but it is not known whether academic stress acts as a risk factor for TB progression on its own or as a confounding factor with poor

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nutrition and inadequate sleep. There is already evidence that TB in adolescents can be prevented and treated, provided that it is identified and treated on time.

The situation of TB burden in China is still significant at the national level, which is a significant challenge for the national TB elimination goal. Primary healthcare (PH) providers perform essential functions in the TB screening, detection and control of TB infections in the community within China's integrated tuberculosis (TB) control system. The prevention of transmission of TB and progression of the disease to adolescent populations is thus an important goal of the national public health system [1].

This systematic review aims to bring all the epidemiological, immunological and clinical evidence on adolescent TB together. It analyzes observations and outbreak data in order to break down connections between academic stress and immune function and its implications for the start of tuberculosis. This work also provides a research context to help resolve some of the causal ambiguities, determine areas of current uncertainty, and guide future epidemiological and mechanistic studies.

2. Adolescent onset characteristics

2.1. Epidemiological evidence

There are significant regional differences in the prevalence of latent tuberculosis infection (LTBI) among Chinese students. Due to the large geographic area and the socio-economic differences in China, it is challenging to establish consistent trends of TB incidence in the different regions. Detection rates for LTBI vary widely within a given city from district to district [2, 3]. There are also differences in screening policies, screening assays and screening frequency that make it difficult to compare screening data between cities. Several testing methods such as tuberculin skin testing, interferon gamma release assays, and imaging of chest X-rays yield varying outcomes of detection that add to the fluctuations in reported estimates of infection.

Geographic variation is not the only group of adolescent TB risk factors. Assuming susceptibility to TB is influenced by academic stress, the prevalence of TB would be higher by age and grade level. Epidemiological investigations of TB among school children invariably conclude that upper grade students are at a greater risk of the disease. The high-risk subgroup is the adolescent in the third year of senior high school (15-17 years). The same age-dependent trends have been observed in different provincial areas. Student cases represent a significant proportion of the total TB reported cases at a national level. The majority of pulmonary tuberculosis among students is found in senior high school students and college students. Passive case detection is still the most widely used identification strategy and can often lead to late diagnosis and the failure to identify early infections.

Greater exposure opportunities can't account for this age-gradient pattern. Although older students attend school for longer periods and have more opportunities to be around others, there is a gradual trend of increasing incidence rates from junior to senior high, corresponding to a gradual increase in academic pressure. As students move closer to university entrance exams, the amount of time spent studying increases each day, the rest time decreases and psychological pressure from the family and school slowly builds. The environmental changes have occurred at the exact time that the number of TB cases has increased. But it is difficult to distinguish risk of exposure from susceptibility of the host, as older students also have higher rates of exposure due to higher rates of boarding and lower rates of health checks than younger students.

Another source of information that provides observational evidence is the seasonal distribution of student TB cases. Case peaks are not evenly spread out over 12 months. There are several regional

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surveillance data sets that show a large peak in the run-up to national high-stakes examinations, and a second peak shortly after the beginning of spring semesters. Inconsistently, fewer numbers are reported during the winter vacation. The reduction in the school holidays implies that there are school-associated factors that play a role in the onset of the disease. During holidays, there is less close contact and less ongoing school pressure; thus, it is hard to determine which of these two factors accounts for the decrease in new active cases. This limitation demonstrates the complexity of separating out the effects of social environment, pathogen transmission and individual susceptibility in the study of TB in this school setting.

2.2. Immunological Specificity in Adolescents

BCG vaccine offers strong protection against severe disseminated tuberculosis in young children, but there is significant loss of protection during adolescence and protection is insufficient in teenage populations against pulmonary TB [4]. More knowledge of adolescent immune physiology is needed to prevent TB in adolescents, as relying on childhood vaccination is not enough. Dynamic changes in the immune system during adolescence involve transformation of T-cell subsets and changes in the population of regulatory T-cells. Intracellular pathogens like Mycobacterium tuberculosis take advantage of this developmental window by decreasing the amount of regulatory T-cells. Immune responses that have been established in adults should not be assumed to be similar in teens, as their immune system is continually adjusting. To better understand how infectious disease severity varies across life stages, we analyzed patients across all diseases and found that severity is higher in adolescent patients. The combination of this innate immune dysfunction and the chronic stress of schoolwork increases the risk of latent infection becoming active tuberculosis.

The adaptive immune system is the main defence mechanism against mycobacteria. Once M. tuberculosis infects humans, the antigen-presenting cells take up the bacterial antigens and stimulate the activation of CD4+ T-helper cells, which coordinate the activation of the macrophages, leading to control of mycobacterial growth within granulomas. The granuloma forms a structure to retain the infection in a latent state, thus preventing the onset of clinical disease. This granuloma control capacity is remodelled in adolescence. The balance of pro- and anti-inflammatory immune responses changes during puberty due to fluctuations in the secretion of sex hormones, which change the profile of cytokines secreted. Since this is a developmental change, there might be a vulnerable window when latent bacteria are not contained by the immune system as strongly as usual when external stressors are applied.

Glucocorticoids disrupt this granuloma stability by suppressing macrophage activation, decreasing pro-inflammatory cytokine production and disrupting T cell differentiation. Exposure to acute stress causes a brief period of heightened cortisol levels, which aids in emergency immune defence, whereas a raised level of glucocorticoids over a long period causes immune system suppression. Stress-induced elevation of cortisol is less severe than when a person takes an exogenous corticosteroid medicine; however, this elevation of cortisol is lasting and happens over the course of months or years during senior high school. While clinical signs of long-term mild immune suppression might not be apparent, there may be a progressive decline in the immune cell control of dormant mycobacteria in granulomas. The gradual decline in immune containment presents a rational biological mechanism by which chronic academic stress might be connected with LTBI reactivation.

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3. Academic stress

3.1. A new species is one that cannot interbreed with any existing species

Academic stress is the physiological, emotional, cognitive and behavioral reactions to stressors in the educational environment which interfere with students' ability to adapt. Academic stress is usually discussed solely in terms of mental health and as a problem only affecting students in the university environment, but here the somatic effects and the downstream risk of infectious diseases are emphasised.

Academic stress is a combination of several factors, including exam anxiety (high-stakes exams), excessive and repetitive homework, lack of sleep (long hours of studying) and societal expectations of academic success [5]. In China, middle school students and senior high school students tend to have to face pressure in the academic aspect, and the pressure is highest in the graduation years. A lack of feedback from teachers can intensify negative emotions such as depression. Chronic stress at the biological level results in activation of the hypothalamic-pituitary-adrenal axis and increased levels of glucocorticoids. Increased glucocorticoids are known to cause immune dysregulation, impairing cell-mediated immunity (CMI) necessary to control mycobacterial growth. Several clinical observations indicate that mental disorders such as depression have a significant impact on the occurrence of tuberculosis reactivation, and therefore mental states can have a detrimental effect on the immune defence against tuberculosis.

TB is a disease with a slow onset and long treatment duration. TB patients are at risk of depression because of disease-related stigma and a diminished quality of life and burdensome treatment schedules. This is accentuated in the adolescent population, in which any academic development is disrupted during treatment. This added stress also further compromises the immune system, creating a vicious cycle.

Lack of sleep is a vital intermediate element to academic stress. Long study hours may lead teens to cut back on the amount of sleep they get each night, which is less than they should be getting based on their age. Sleep directly contributes to the consolidation of memory and regulation of cytokines. Sleep deprivation itself can harm cellular immunity and can increase inflammatory imbalance. The examination pressure is a major confounder as it is highly similar to sleep loss. Academic stress and sleep deprivation are often present and both can alter anti-TB immunity. Research on their individual effects is ongoing, which is why it remains unclear if academic stress is a separate factor or one that works in conjunction with sleep deprivation and inadequate nutrition.

Psychological distress also modifies health behaviours. Those students under a lot of pressure may cut back on exercising or eating meals or have an unbalanced diet. Reduced activity leads to reduced overall immune fitness and insufficient nutrient intake reduces the production of immune cells. These changes in behaviors are the secondary effects of the academic pressure and are the basis for a multilevel pathway leading towards increased susceptibility to TB. This cascade shows that academic stress can affect the risk of TB by direct neuroendocrine effects as well as indirectly by affecting lifestyle and nutrition [6].

3.2. The outbreak cases of tuberculosis were analyzed

The time trend of cases of TB shows a temporal clustering with the peak in June when the national college entrance examination was held. This is a June peak that has been documented repeatedly in the local surveillance records over multi-year monitoring periods, as well as a secondary peak at the start of spring semesters and lower case numbers during the winter vacation. Such a trend indicates

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that the greater pressure students face during their academic studies when they are about to take their exams can make them more susceptible to disease progression.

Boarding school settings are also known to be a potential high-risk environment for TB outbreaks. One case of pulmonary TB was once identified in a large group of contacts in a single senior class of a boarding high school, resulting in a high attack rate in the affected class. Some of the main reasons were lack of morning health checks, poor absenteeism follow-up, and lack of adherence to standard screening processes and delayed preventive treatment. Overcrowding in dorms, as well as inadequate ventilation and health check-ups in dorms, facilitate the spread of pathogens. Adolescent wellbeing is another factor that is associated with the risk of major outbreaks when poor attention to wellbeing is given [7-10].

Some boarding schools have had repeated outbreaks and very high attack rates at the class level in the affected cohorts. Persistent issues found in retrospective investigations include delay in diagnosis, incomplete population screening, and inadequate preventive intervention. Recurring outbreaks indicate structural gaps and weaknesses, and thus a need for continued public health focus. Examples of boarding school outbreaks are good examples of the interplay of transmission opportunity and host susceptibility. Dormitories and classrooms provide opportunities for close and long contact situations which facilitate the transmission of airborne mycobacteria.

4. Conclusion

This paper explores the potential association between academic stress and active tuberculosis development among adolescent populations. Adolescents possess incompletely mature immune systems while enduring heavy academic pressures from examinations, extensive homework, sleep deprivation and societal expectations. Epidemiological evidence shows TB risk rises alongside grade level, with case peaks occurring during national college entrance examination periods. Clustered outbreaks in boarding schools repeatedly reveal diagnostic delays, incomplete screening and inadequate preventive care. Collectively, these observations suggest academic stress may function as an independent susceptibility factor beyond co-existing variables such as inadequate nutrition and poor sleep. Chronic academic stress triggers HPA-axis activation and glucocorticoid elevation, inducing depression and immune dysregulation that impair host immune defence against Mycobacterium tuberculosis. Adolescent patients face lengthy treatment that interrupts academic progression and creates further stress, forming a self-amplifying vicious cycle. The findings of this review are constrained by several key limitations, including insufficient molecular mechanistic evidence, absence of original experimental data, unresolved confounding effects and reverse causation risks. Therefore, conclusions are tentative and require further targeted research to validate the proposed causal pathway.

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