BOLD in Africa: What has it taught us?

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Abstract

The Burden of Obstructive Lung Disease (BOLD) study was set up with the primary objective of measuring the prevalence of Chronic Obstructive Pulmonary Disease (COPD) and its risk factors around the world. With the exception of one centre in South Africa, centres in Africa were only recruited in a second phase funded by the Wellcome Trust after 2006. So far, there is no reason to believe that the causes of chronic airflow limitation act differently in Africa than elsewhere, though exposure to these does vary considerably across the continent. Smoking is still a major cause of airflow limitation wherever smoking is prevalent. A history of tuberculosis is also strongly associated with airflow limitation as well as with the restrictive pattern that might be associated with loss of lung tissue. There has been no association found with the burning of biomass fuels. Although a surprise to some people, this is consistent with the low prevalence of chronic airflow limitation (CAL) in areas where biomass fuels are commonly used for cooking and heating and with the results from another much larger study in China. Other topics that still need to be fully explored in the African context are the risks posed by occupational exposures and the potential role of asthma as a risk for chronic irreversible obstruction in later life. Most of the indications are, however, that the high prevalence of low lung volumes is a greater problem in much of sub-Saharan Africa than airflow obstruction. A full interpretation of this finding will need to wait for the outcome of the BOLD II study that is just starting.

The origins of BOLD

The Burden of Obstructive Lung Disease (BOLD) study was set up under the leadership of Sonia Buist with the primary objectives of: 1) measuring the prevalence of Chronic Obstructive Pulmonary Disease (COPD) and its risk factors in various areas around the world; 2) estimating the burden of COPD in terms of its impact on quality of life, activity limitation, respiratory symptoms, and use of health-care services; and 3) developing a model to project future burden of disease for COPD.[1] Secondary objectives included: 1) comparing different diagnostic criteria for COPD; 2) determining the extent to which variations in risk factors contribute to variations in the prevalence of COPD; 3) describing the distribution of COPD according to age, sex, and smoking history; 4) describing the main clinical symptoms reported by subjects diagnosed with COPD; 5) assessing the sensitivity and specificity of selected clinical symptoms for COPD using lung function testing as the gold standard; and 6) characterising the clinical management of COPD in selected broad geographic areas.

Although a site in the Western Cape in South Africa was among the earliest to be recruited into the study, the majority of the sites in the early years of the study were in Western Europe. When the initial funding ran out, the Wellcome Trust provided funding with the specific objective of extending the work to low- and middle-income regions of the world, and further study sites were recruited in Africa both north and south of the Sahara.

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What we thought that we knew about COPD in Africa

In 2009 a systematic review of the literature was not able to identify any estimates of airflow obstruction based on spirometry from general populations in sub-Saharan Africa with the exception of the results from the BOLD site in the Western Cape.[2] What was known was based on selective samples of 'at risk' populations. The same authors reported on a survey of Pan African Thoracic Society members and concluded that many did not have access to spirometry and had to rely on symptoms to make a diagnosis of COPD. The most comprehensive information on disease burden was the Global Burden of Disease (GBD) study which relied predominantly on World Health Organisation estimates of mortality from different conditions to provide local data on disease impact. This provided high estimates of the impact of COPD in low-income countries, including much of sub-Saharan Africa.[3]

The high mortality estimated in sub-Saharan Africa and also in South Asia was surprising in the absence of widespread use of tobacco products which have been regarded as the main cause of airflow obstruction in the West. This led to speculation about other potential causes of obstruction, including most prominently high levels of indoor air pollution from cooking stoves.[4] Other potential risk factors included occupational exposures in poorly regulated industries.

Defining COPD and chronic lung disease – GOLD and all that jazz

Even where the data do exist the definition of COPD is problematic. The first difficulty is that the term is used for a clinical diagnosis and clinicians have been reluctant to give a clear

definition. The Global Initiative on Obstructive Lung Disease (GOLD) guidelines state that 'Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.'[5] This may be a good description of what the authors agreed to be common features of the condition but it falls a long way short of being a useful definition. It gives no unambiguous criterion by which a decision can be taken as to whether an individual does or does not have 'COPD'.[6]

Many clinicians have been reluctant to provide a less ambiguous definition based on spirometry alone. Nevertheless, without a precise definition a cogent study of the condition is impossible. Many have got around this problem by defining COPD in terms of spirometry alone while acknowledging that this is not quite the same thing as clinical COPD. To make this distinction clear it is helpful to reserve the term 'COPD'for a clinical diagnosis, acknowledging that it is a rather vague and flexible concept open to variable interpretation, and use an alternative term such as Chronic Airflow Limitation (CAL) for a condition defined entirely by spirometry.

The definition of chronic airflow limitation is also subject to controversy. The usual measurement of obstruction is the ratio of the 1-second Forced Expiratory Volume (FEV_1) to the Forced Vital Capacity (FVC). Although there are legitimate alternatives to this measurement, it is a common error to believe that a low FEV_1 by itself is a measure of airflow obstruction. This is because a low FVC will also lead to a low FEV_1 even in the absence of obstruction. Disagreements have arisen over how to define a 'low'FEV_1/FVC ratio. GOLD have suggested that a fixed cut off of 70% should be used; others such as the European Respiratory Society and the American Thoracic Society have preferred to use the value that is exceeded by 95% of the population who don't smoke, don't have respiratory symptoms and don't have a respiratory diagnosis – defined as the 'normal'population. Finally, when defining 'normal'populations there are disagreements over which 'normal'population should be used. The 'normal'population (as defined above) of African Americans (for instance) has a lower FEV_1 and a lower FVC than the normal population of white Americans. Differences are much less marked for the FEV_1/FVC ratio. Different authors have recommended using a single common standard, a limited selection of regionals standards or local or national standards.

Chronic Airflow Limitation and its distribution

So far there has not been a co-ordinated publication of the BOLD data from Africa and the early multi-site papers with general information on distribution using common criteria included only data from Cape Town[7-9] and Sousse.[8] These showed extreme variation. In Sousse the prevalence of a FEV_1/FVC ratio below the lower limit of normal was 8.6% among men and 1.8% among women, whereas in Cape Town these rates were 23% among men and 16.8% among women. Other reports have used slightly different criteria but have tended to show low levels of obstruction, 6.9% overall in Ile-Ife Nigeria[10] using a similar lower limit of normal, 6.4% in Annaba, Algeria[11] and 3.4% of 'moderate to severe'obstruction in Blantyre Malawi using a rather more restrictive definition.[12] To put these figures into perspective, the definition of the lower limit of normal includes 5% of the normal, asymptomatic non-smoking population and so determines an expected minimum prevalence of 5%. These low prevalence rates are at odds with the high mortality rates reported by the global burden of disease.[3] A recent report from Tanzania using the BOLD protocol has suggested a much higher prevalence of obstruction, but this is based on a fixed cut-off of 70% for the FEV_1/FVC ratio and is confined to the older population (over the age of 40 years) where a FEV_1/FVC ratio of 70% may be normal.[13] As presented these data are hard to interpret.

Association with smoking

Early publications from BOLD showed the expected association between airflow obstruction and smoking history.[7, 9] The effect was slightly greater in women than in men but was remarkably consistent wherever it was measured. The low prevalence rates of chronic airflow obstruction found in all the African sites with the exception of the Western Cape are entirely consistent with the relatively low prevalence of smoking among the older age groups that were studied by the BOLD sites (40 years and over). An analysis of some of the early BOLD sites also supports the view that there is an association between the exposure to tobacco and the prevalence of airflow obstruction.[8] A word of warning needs to be inserted, however. The BOLD study only examined lung function in those aged over 40 years. On the current evidence, younger cohorts, if they smoke more, will be at equal risk to the cohorts in the Western world that were devastated by the effects of tobacco from the middle years of the twentieth century.

Association with TB

Reduced lung function was also strongly and consistently associated with a self-reported history of tuberculosis. The association was as strong or stronger with airflow obstruction (adjusted odds ratio 2.51,95% CI 1.83–3.42) as with spirometric restriction (adjusted odds ratio 2.13, 95% CI 1.42– 3.19).[14] The estimated effect on obstruction was far less variable from site to site than was the effect on restriction and was possibly also less variable in the low-income than the high-income study centres. This effect was clear in the results from Cape Town, the only sub-Saharan site in the general BOLD analysis. It was very similar (though not in itself significant) in Annaba and although it was estimated to be much lower in Fes the confidence intervals were very wide and quite consistent with the overall result. Since that analysis the site in Ile-Ife has also reported a significant association with a history of tuberculosis;[10] the site in urban Malawi has not, though the prevalence of a self- reported history of TB was low.[12] Given the strength and consistency of the association between TB and chronic obstruction and the relatively high prevalence of past tuberculosis in Africa, we can expect that this will have a serious impact on the prevalence of the disease. This has important implications for the follow up of TB patients after treatment.[15]

Association with biomass

There is a strong belief that household air pollution from burning biomass fuels is a common cause of 'COPD' in Africa and in low-income countries generally.[4] The evidence is surprisingly weak. The WHO's review of the evidence on which much of this assessment is based concedes that the 'there was strong evidence of publication bias (Egger's test: $p = 0.007$); the pooled OR was 1.94 (1.62, 2.33) with substantial heterogeneity (I^2 =85%).'[16] The strong evidence of publication bias and the very high level of heterogeneity would each on their own suggest the lack of a direct causal association, or even the lack of evidence for any association at all. Consistent with this the BOLD study found no good evidence of any association. We found no association between airflow obstruction and use of solid fuels for cooking or heating (OR_{men}=1.20, 95%CI 0.94-1.53; OR_{women}=0.88, 95%CI 0.67-1.15). This was true for low/middle- and high-income sites. Among never smokers, there was also no evidence of an association of airflow obstruction with use of solid fuels (OR_{men}=1.00, 95%CI 0.57-1.76; OR_{women}=1.00, 95%CI 0.76-1.32).[17] Although this result was criticised on the grounds that the exposure had not been measured other than from a history of personal use of these fuels, there is little reason to believe that the relevant exposure (a decades long exposure or more) is better assessed by current exposure to measured particles. Additional arguments for believing this negative result are the lack of any increase in the prevalence of obstruction in centres that had a high use of biomass fuels for cooking, and a similar negative finding for an even larger study in China.[18] Although it is possible that a high prevalence of airflow obstruction due to the use of biomass fuels was masked by a compensating absence of some other powerful risk factor such as smoking the very low prevalence of obstruction in many of those centres using biomass most heavily (often below what would be expected in a healthy non-smoking population) makes this an unlikely explanation.

Association with occupation

There is also a strong belief that occupation may play an important role in the development of chronic obstruction, though reviews of the evidence in the developed economies with regard to general exposures to occupational dust and fumes (as distinct from exposure to specific dusts) have come to very different conclusions.[19, 20] Nevertheless an early BOLD analysis reported a significant reduction in the FEV1/FVC ratio (-0.33% (95% CI: -0.50%, -0.15)) for every ten years exposed in a dusty job, though there was not a significant increase in the prevalence of CAO associated with this exposure.[9] It is often speculated that lower standards of worker protection in some low-income countries might put workers at particular risk, but so far the evidence has not been fully explored in the BOLD sites in Africa and the individual sites that have reported results have probably not had the power on their own to detect any likely effect.[10, 12]

Association with poverty

An early ecological analysis of BOLD data showed a strong association between the gross national income of the country and the mean level of the Forced Vital Capacity in the BOLD sites in that country. There was little evidence for a strong effect of poverty on the FEV1/FVC ratio. With the later BOLD sites we introduced a wealth score based on household assets (21) and have since analysed the association of poverty in the later centres which have collected this more detailed information. Following adjustments for age and sex, FEV_1/FVC increased by 0.36% (absolute change) (95%CI: 0.22, 0.49; p<0.001) per unit increase in wealth score. Adjustments for other confounders reduced this effect to 0.23% (0.11, 0.34), but even this value remained highly significant (p<0.001). Results were consistent across sites (I^2=1%; p_{het}=0.44) and at the ecological level mean wealth scores explained 38% of the variation in mean FEV1/FVC between sites (r^2=0.385, p=0.031).[22] These results were adjusted for smoking, education, working in a dusty job, a history of tuberculosis and other potential confounders and we do not have a clear idea of the nature of the residual association with poverty nor of the overall impact of poverty on the prevalence of CAL in Africa. A better understanding of this is likely to emerge with the further analysis of the data from Africa and elsewhere.

Association with asthma

Asthma and COPD are regarded as quite different conditions, but it is increasingly suspected that chronic asthma may develop into irreversible obstruction and so can be a cause of chronic airflow limitation.[23] The reasons for this are unclear, though it seems that it is not explained by the prevalence or severity of the atopic condition of the patients.[24] In BOLD we only have information on the self-reported diagnosis of asthma and this may be hard to interpret, but in the Nigerian study there was a strong association between chronic (post-bronchodilator) airflow obstruction and a diagnosis of asthma. It will be important to investigate this further.

Is Africa (or sub-Saharan Africa) a special case?

The results from BOLD Studies in Africa are still only partially reported and it would be foolish to make too many predictions. So far, however, it seems likely that disease behaves very much as it does in other parts of the world, and in particular in other low-income settings in Asia. Africa itself is a large and diverse continent including the countries of the Maghreb, which have more in common with Western Asia, and the Sudan which has characteristics of both regions. The South African BOLD site is exceptional even by South African norms. What will certainly be different will be the risks to which the populations are exposed and these are likely to be individual to each population.

Nevertheless the chronic lung disease that is seen in low-income countries, including most of sub-Saharan Africa and much of Asia is very different to that currently seen in the developed economies of the north. The abiding difference is not in the level of obstruction – which, so far, is largely absent – but in the low lung volumes. The relevance of the difference in FVC between different ethnic groups is disputed. Some believe that these differences should be discounted as being normal variation. The evidence from America, however, is that the lower FVC in African Americans is associated with the same high mortality rate as would be predicted for a white American population that had the same values of FVC.[25] Although the accepted wisdom is that these levels are 'normal', it is only true in the sense that they

are 'usual'. The assumption that these levels are determined by 'genetics' or race is no more than an assumption[26] and, whatever the causes of the low lung volumes, it appears that the consequences are serious. If mortality rates among black Americans are equal to those of white Americans of the same vital capacity, age, sex and height, then the low vital capacity among black Americans should be a matter of more critical interest than it has been to date, and the reasons for the low vital capacity seen among all other low-income groups in Africa and Asia ought to be a major and urgent focus of research. The descriptive data from the BOLD study will make a major contribution to defining these research questions.

Author declaration

There are no competing interests to declare.

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