SCIENTIFIC PAPER COMPETITION – AUSTRALIA

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Type 2 Diabetes Mellitus in Alcoholic Liver Disease - The Road Less Travelled

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Background

Alcoholic liver disease (**ALD**) is a major cause of chronic liver disease in Australia. Unfortunately, about 20% of Australian still consume enough alcohol to put them at risk of developing alcohol related injuries, which includes ALD. On the same note, ty pe 2 diabetes mellitus (**T2DM**) is also a prevalent chronic disease, which incidence has been rising. A recent study has found that the prevalence of T2DM in ALD is more significant compared to the general population. Furthermore, while it is known that high blood glucose levels are associated with a worse fibrosis score, there has been no study done to explore the association of T2DM and the overall progression in ALD. We aim to review the effect of co-morbid T2DM on the liver function of patients with ALD, an d to discuss the implications on patient management.

Material and methods

A comprehensive literature search for relevant articles from inception to December 2013 was performed on MEDLINE, Sc opus and Discovery for original research and review articles using the key words: "Liver Diseases, Alcoholic" and "Diabetes Mellitu s, Type 2". Data were synthesised (after filtering by exclusion criteria) from 13 quantitative studies that explored the relationship b etween ALD and T2DM co-morbidity.

Results

While not many studies have looked into how T2DM affects the progression of ALD, it is well-established that T2DM wor sens progression of chronic liver diseases in general. Furthermore, T2DM and ALD synergistically increase the risk of developing h epatocellular carcinoma. There is no direct evidence in the literature that looks into how T2DM affects LFT values in ALD, however it was found that in obese patients, a lower dose of alcohol is required to elevate gamma-glutamyltransferase (**GGT**). This indicate s that there is an unexplored territory in the assessment and management of patients with T2DM and ALD, which warrants explor ation.

Conclusion

Our review of the literature yielded few results regarding the effects of concurrent T2DM and ALD on liver function. Give n the potential for patients to suffer worse liver outcomes should these conditions occur together, we consider this to be a notab le gap in the literature. As such, our paper should serve as a foundation to future research in this area in order to develop effecti ve prevention and management strategies for the co-occurrence of these conditions.

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Introduction

Alcoholic liver disease (ALD) is an important chronic disease in Australia, which is characterised by long-standing hepatocellular damage as a result of excess alcohol consumption. ALD represents a spectrum of liver diseases - steatosis, steatohepatitis and cirrhosis as well as acute alcoholic hepatitis (O'Shea, Dasarathy, & McCullough, 2010).

According to the 2010 Drug Strategy Household survey, alcohol was consumed by 80.5% of Australians over the age of 14 in the last 12 months. Although there is a declining trend of alcohol consumption in comparison to 2007, in 2010 1 in 5 people still consumed alcohol in a high-risk pattern that may result in acquisition of alcohol-related diseases (including traumatic injuries) over their lifetime (AIHW, 2008). The consumption of alcohol for the population over 15 years of age is estimated to be 10 litres per capita in Australia, (OECD, 2013) with males being more likely to be regular drinkers (AIHW, 2008).

The prevalence of ALD itself is difficult to determine as most cases are diagnosed late in the course of the disease. In 2012, it was estimated there were at least 6,203 alcohol-related liver disease cases in Australia. An addition of more than 1,000 new cases are expected by 2030 (GESA, 2013).

The pathophysiology of ALD is not completely understood (Testino, 2013). However, two key mechanisms of damage due to chronic alcohol consumption have been proposed. Firstly, it is well-accepted that alcohol consumption (ethanol) causes oxidative stress and inflammation of the hepatocytes, leading to liver damage (Testino, 2013). This is mediated by the generation of reactive oxygen species as a by-product of ethanol metabolism, which causes mitochondrial glutathione (an anti-oxidant enzyme) depletion, culminating in sensitization of hepatocytes to injury.

Secondly, alcohol consumption promotes enteric bacterial overgrowth and increases gut mucosal permeability, which increases the translocation of endotoxin (bacterial lipopolysaccharide molecules) to the bloodstream, and subsequently to the liver. These two pathological mechanisms result in alcohol-induced complement activation in conjunction with endotoxin-mediated Kupffer cell activation (via TLR4). These activated Kupffer cells consequently release TNF-α, a pro-inflammatory cytokine, which induces hepatocyte injury (Gao &Bataller, 2011). While Kupffer cells are also known for its role in initiating hepatoprotective (regenerative and anti-inflammatory) responses through the same pathway, these mechanisms seem to be inhibited in chronic alcohol consumption (Gao &Bataller, 2011). In summary, the imbalance between anti-oxidative mechanisms and oxidative stress imposed on hepatocytes in chronic alcoholism, in association with the release of inflammatory mediators due to endotoxemia are the principal mediators for the progression of ALD.

A few established risk factors have been documented in the literature for ALD. Non-modifiable risk factors include gender (women develop more severe disease than men, even with lower absolute amount of alcohol consumption) and genetic variations (e.g. PNPLA3 variant) (Testino, 2013; Tian, Stokowski, Kershenobich, Ballinger, & Hinds, 2010). Modifiable risk factors include smoking (Altamirano&Bataller, 2010) and indeed, aggressive drinking behaviours such as binge drinking and chronic high dose consumption (> 10 years) (Testino, 2013).

Type 2 Diabetes Mellitus (T2DM) is considered to be an epidemic in Australia, with an estimated 848,000 Australians currently suffering from the condition. Furthermore, from 1989 to 2012, the number of diabetes diagnoses (T1DM and T2DM) has almost tripled (AIHW, 2013).

Interestingly, the Australian Bureau of Statistics have reported that up to 10.7% of Australians with T2DM (which approximates to ~85,000 people) display high-risk alcohol drinking behaviour (Australian Bureau of Statistics, 2011). This fact, supported by a parallel of epidemics of ALD and T2DM means that more patients with the dual diagnosis of ALD plus T2DM (ALD-T2DM) will be encountered (GESA, 2013). Their co-existence in one patient may prove to be catastrophic, as they independently increase the risk of poor liver outcomes (Hickman & Macdonald, 2007; Testino, 2013).

Only a single study has been documented in the literature which examines the relationship between ALD and T2DM. Kotronen et al.(2010) and colleagues in her study found that the prevalence of T2DM in alcoholic fatty liver disease (a component of ALD) approximates that in non-alcoholic fatty liver disease (NAFLD) at ~25%, which is much higher than that in the general population. In light of this, our paper will attempt to review the relationship between T2DM and ALD by examining liver outcomes in terms of liver function tests (LFTs) and a subsequent complication of hepatocellular carcinoma (HCC). Improved management options will be discussed in relation to an anticipated worse prognosis in patients with dual diagnosis.

Material and Methods

Our selection criteria included quantitative studies that explored the relationship between ALD and T2DM. We excluded studies that did not elicit relevant data, qualitative studies, duplicate articles, conference abstracts and non-English articles (due to a lack of access to translation resources). A comprehensive literature search for relevant articles from inception to December 2013 was then performed on MEDLINE, Scopus and Discovery (The University of Melbourne) for original research and review articles using the key words: "Liver Diseases, Alcoholic" and "Diabetes Mellitus, Type 2". In addition, a manual search was performed via Google Scholar and for the reference lists of relevant studies and reviews. Our initial search yielded 1243 articles for abstract screening. Of these, 12 studies were included in our review following assessment of the full-text articles. Studies selected for analysis were further divided by topic: data on LFTs, HCC, or articles presenting known data on comorbidity between ALD and T2DM. Researcher triangulation was achieved through having multiple investigators appraise and synthesise the evidence from each article.

Results

1. Liver Function Tests (LFTs)

A. Gamma-GlutamylTransferase (GGT)

Whilst GGT levels are only moderately correlated with excessive alcohol consumption (Conigrave, Davies, Haber, & Whitfield, 2003), GGT was found to be markedly elevated in ALD as an established diagnosis (Kojima et al., 2005). Moreover, compared to non-alcoholic steatohepatitis (NASH), the average GGT level in ALD is significantly higher (NASH: 68.7 IU/L vs ALD: 496.9 IU/L) (Kojima et al., 2005). Interestingly, it has been found that in people with baseline obesity, GGT increases with just mild alcohol consumption (Conigrave et al., 2003).

B. The Transaminases - Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT)

ALT is more specific to the liver than AST by histopathological evidence. Across the spectrum of ALD, alcoholic fatty liver disease only causes minimal elevation, while in alcoholic hepatitis, the value goes up to 500 U/L (Conigrave et al., 2003). This is also supported by another study, in which aminotransaminases were found to be only slightly elevated in ALD patients without hepatitis (mean AST 54.1 U/L, ALT 72.8 U/L), but were grossly increased in those with alcoholic hepatitis (mean AST 668.2 U/L, ALT 399.8 U/L). On the other hand, NASH exhibits a similar slight elevation pattern of aminotransaminases as alcoholic fatty liver disease without co-occurring hepatitis (mean AST 67.2, ALT 117.6)[ASH vs. NASH]. Importantly, in advanced disease with liver failure, these markers are not reliable in indicating liver damage (Conigrave et al., 2003).

In a study where patients with T2DM were screened, up to 28% of patients demonstrated generalised elevation of LFT results. Of these, 65% were subsequently diagnosed with NAFLD and 87% demonstrated steatosis by ultrasound criteria [**Figure 1 and 2**] (Hickman, Russell, Prins, & Macdonald, 2008). Another study further showed that worse LFT profiles are seen in T2DM patients with ultrasound evidence of steatosis (ALT, AST = 36.16, 38.35) compared with those without (AST, ALT = 19.61, 24.57) (Krishnan. &Venkataraman., 2011). Our search did not retrieve studies that directly look at how T2DM influences LFT results in ALD.

2. Hepatocellular Carcinoma (HCC)

Daily ethanol consumption of ≥80mL and ≥160 mL results in an exponential increase in the risk of a person developing HCC 5-fold and 25 fold, respectively (Hassan et al., 2002). Whilst impact on T2DM alone to the risk of HCC is not well-documented, there are three studies to support the notion of excess risk of HCC in patients with a liver disease plus co-morbid T2DM. A study has reported a 10-fold increase in the risk of progression to HCC when T2DM is combined with viral hepatitis and hazardous drinking (Hickman & Macdonald, 2007). Balbi et al. (2010) further documents an increased risk of HCC in the presence of both T2DM and alcohol consumption (OR = 49.0 with (CI 21.5−111.8; P < 0.0001)) comparatively with alcohol consumption alone (OR = 3.7 with (CI 2.5−5.4; P < 0.0001) [**Figure 3]**. Finally, a statistical calculation by Hassan et al. (2002) indicates Synergy Index between alcohol consumption and diabetes in increasing HCC risk with a result of 2.9 (1.3-4.6).

3. The Relationship between T2DM and ALD

It has been noted that there is a bidirectional relationship between ALD and T2DM (Hickman & Macdonald, 2007).

First, we examine the impact of ALD on glucose tolerance and development of T2DM. Even in terms of simple alcohol consumption, Garcia-Compean et al(2009) reports a 2-fold increase of T2DM risk in patients who consume alcohol ≥270 gram/week compared with those who consume ≤120 gram/week (Garcia-Compean et al., 2009). Not surprisingly, patients with chronic liver diseases (CLD) are prone to developing diabetes, as demonstrated by the following two studies. (Holstein et al.(2002) found that 96% of their patients with cirrhosis have impaired glucose tolerance (IGT), of which 75% suffer from T2DM. In another CLD study, where ALD diagnosis makes up 74.3% of the study participants (of variable degree of disease severity), IGT was also demonstrated. In patients with severe disease, 69.8% was found to have IGT, with 17.4% with diabetes (Mukherjee., Sarkar., Das., & Banerjee., 2013).

Secondly, there exists some evidence in the literature that elucidate the impact of T2DM on liver function and development of ALD. One study showed that high blood glucose level is a risk factor for hepatic fibrosis ($p<0.05$). This applies both in ALD patients with (r = 0.11 +/- 0.05; P = .027) or without (r = 0.115 +/- 0.045; P = .011) cirrhosis (Raynard et al., 2002). This is consistent with Garcia-Compean et al. (2009); Hickman & Macdonald.(2007) andPicardi et al. (2006) who emphasized that presence of insulin resistance is a risk factor for the progression in any liver disease (not only limited to ALD) (Garcia-Compean et al., 2009; Hickman & Macdonald, 2007; Picardi et al., 2006).

Discussion

1. Interpretation of the Results

Our paper is amongst the first to review the relationship between ALD and T2DM. Here, we evaluate the disease outcomes of ALD alone, T2DM alone and ALD-T2DM in the literature and have found the results to be alarming.

First, our review has confirmed the bidirectional relationship between ALD and T2DM; each seems to be a 'cause' as well as a 'consequence' of the other (Results - 3). This should alert the medical community that the two might co-exist in one patient whenever we are making one diagnosis or the other. Management options therefore, have to take both diseases into account as will be discussed below.

Secondly, by LFT parameters, most intriguing is the fact that a proportion of T2DM patients, upon general screening with LFTs (+/- ultrasound), may inadvertently be found to have NASH (Results - 1). This might be an incentive for inclusion of routine LFTs (+/- ultrasound) in each medical consult of T2DM patients.

Finally, the evidence of synergy between ALD and T2DM in the development of HCC, a leading cause of death due to liver diseases, should be a strong reason why we need to improve vigilance in monitoring for the development of T2DM in our ALD patients, and vice versa (Results - 2).

2. Current method of management of ALD

Treatment regimens for ALD depend on the severity of disease, which can be determined using scoring systems such as the Glasgow Alcoholic Hepatitis Score o r MELD score, amongst others (Lucey, Mathurin, & Morgan, 2009).

Nevertheless, the management of alcoholic hepatitis encompasses three main goals: stabilisation of general health, reduction in inflammation and cessation of al cohol consumption.

One essential aspect of stabilisation of general health is through nutritional supplements to compensate for chronic alcohol abuse-related malnutrition (Menden hall, Anderson, Weesner, Goldberg, &Crolic, 1984). Mendenhall et al.(1984) reported that protein-calorie malnutrition is correlated with increased mortality, severity of liver d isease and hepatic dysfunction. Logically, improved nutritional status should correlate with improved survival. However, a Cochrane review

noted there was no evidence to justify the use of nutritional supplements in liver disease patients (including alcoholic hepatitis) (Koretz, Avenell, &Lipman, 2012). Despite this evidence, Australian general practitioners (GPs) still emphasise the use of a high energy, high protein diet (1-1.5 grams of protein per kilogram bodyweight) alo ng with supplemental vitamins such as thiamine and folate for ALD patients (Duggan. & RACGP, 2011).

Reduction in inflammation is achieved predominantly through pharmacological methods. The Australian therapeutic guidelines recommend prednisolone (50mg daily for 28 days, with a gradual reduction over 3 weeks) (eTG, 2013). However its use remains controversial with only 40% of patients responding to steroids and many oth ers having contraindications to therapy (Lucey et al., 2009). In addition, a 2008 systematic review demonstrated insufficient evidence to recommend or refute glucocorticoid therapy (Rambaldi et al., 2008). The meta-analysis however demonstrated statistical heterogeneity ($P < 0.05$ and $I2 = 49.7\%$), differing inclusion and exclusion criterion of in dividual studies, poor methodology and low trial numbers. Nevertheless, glucocorticoids are still a mainstay of treatment of ALD.

The final and arguably, the most important, intervention focuses on alcohol abstinence as it has been linked with improved clinical outcomes and lowered risk of progression to cirrhosis. Principle issues that must be addressed include physiological dependence (including withdrawal symptoms), psychological dependence and the br eakdown of daily routine of alcohol drinking (Enoch & Goldman, 2002).

During the acute phase of alcohol abstinence, withdrawal symptoms often occur, ranging from diaphoresis and tachycardia, to generalised tonic-clonic seizures a nd delirium tremens (Roffman. & Stern., 2006). Hence, benzodiazepines are recommended in Australia to alleviate and prevent these symptoms (eTG, 2013).

Subsequently, maintenance of alcohol cessation involves both pharmacological and non-pharmacological therapy. Pharmacologically, both naltrexone (opioid ant agonist) and acamprosate (central nervous system inhibitor) have been shown to reduce cravings and withdrawal symptoms (O'Shea et al., 2010), with one recent study con cluding that combination of the two yields better results than either drug alone (Feeney, Connor, Young, Tucker, &Mcpherson, 2006).

Non-pharmacological approaches such as motivational interviewing (MI) and cognitive behavioural therapy (CBT) are also employed to address psychological de pendence. MI engages a patient's intrinsic motivation to change their behaviour (Burke, Arkowitz, &Menchola, 2003), with research demonstrating it most efficacious as a pr eamble to more formal psychotherapies. Its effects only persist for six months after cessation of treatment (Noonan. & Moyers., 1997). In the long term, CBT is widely utilise d, helping patients to identify and alter negative thoughts (Longabaugh et al., 2005). This therapy is based on the idea that a patient's actions are dictated by situational fe elings, and that identifying and reducing the impact of stressors can negate the chance of relapse (Longabaugh et al., 2005).

Finally, for patients with alcoholic hepatitis that progress to liver failure, the only cure that remains is liver transplantation. Left untreated, prognosis is extremely poor with 8% of patients dying each year whilst waiting for a transplant (TSANZ, 2011). Australian transplantation guidelines stipulate that potential recipients must demon strate 6 months of alcohol abstinence and have a low risk of continued alcohol abuse (TSANZ, 2011). Patients are categorised based on a routinely-updated Australian guid elines with urgency of their need as a key criteria. Key exclusion criteria include liver-intrinsic factors such as metastatic HCC and persisting alcohol abuse as well as general factors such as poor cardiovascular health (TSANZ, 2011).

3. Current method of management of T2DM

The key objectives for T2DM management include symptom relief, prevention of disease progression and or complications, as well as maintenance of quality of l ife (IDF, 2012). As will be discussed below, there are four domains of management which are considered to be fundamental in achieving these aims. A further level of compl exity arises when considering patients with underlying ALD

Weight loss is arguably the most important step in T2DM management. The most recent statistics reveal that about 80% of Australians with diabetes are overwei ght (AIHW, 2008). Thus, a referral to a dietician and consumption of a low-calorie, low-fat and high-fibre diet should be encouraged. Additionally, the consumption of low g lycaemic index (GI) carbohydrates [**Figure 4**], which contribute to a progressive, sustained rise in blood glucose is essential for two reasons: stable blood glucose levels redu ce the risk of hypoglycaemic complications and post-prandial glucose is a major contributor to HbA1c% (Monnier, Lapinski, & Colette, 2003), which needs to be kept as low as 7.0% to reduce vascular complications (DCCT, 1993). As an adjunct to dietary control, regular exercise has also been shown to improve blood glucose levels (McCulloch, 2013). Exercise regimens should be constructed under the guidance of health professionals to avoid hypoglycaemia (IDF, 2012).

Secondly, pharmacotherapy is used if lifestyle modification measures prove to be unsuccessful. There are various available medications, however Metformin® is c onsidered as first line therapy, followed by the sulfonylureas. Insulin therapy is implemented if the treatment target for blood glucose levels is still not achieved (IDF, 2012) [**Figure 5**]. In addition to glycaemic control, other cardiovascular

disease (CVD) risk factors such as hypertension, dyslipidaemia, smoking and excess alcohol consumption need to be addressed simultaneously using conservative and/or medical treatments (McCulloch, 2013).

Thirdly, due to the multiple complications that can arise from chronic hyperglycaemia, it is important to ensure that there is close multi-professional monitoring of patients with T2DM. Generally divided into microvascular and macrovascular domains, the former often comprises of the triad of diabetic retinopathy, nephropathy and neuropathy, whilst the latter encompasses the effects of atherosclerosis on major blood vessels in the body [**Figure 6]** (Fowler, 2011). Regular follow-up for retinopathy and nephropathy by an ophthalmologist and a GP/nephrologist, respectively, are required to prevent the sequelae of blindness and microalbuminuria or overt proteinuria (IDF, 2012). The latter is particularly important as microalbuminuria is an independent risk factor for CVD (Sarnak et al., 2003). Additionally, close follow-up of foot health by a podiatrist is recommended for all T2DM patients, as peripheral vascular disease, in conjunction with peripheral neuropathy, is responsible for diabetic foot disease. Often exacerbated by the immunosuppressive nature of diabetes, this is a condition where there is a vicious cycle of unrecognized damage due to loss of sensation, with potential subsequent infection that fails to heal due to inadequate vascular supply (Cheer, Shearman, & Jude, 2009). With all these complications, it is important to reiterate that good glycaemic control is the mainstay for prevention and treatment (UK Prospective Diabetes Study Group, 1998).

Finally, patient education is crucial in the success of diabetes management. Ideally carried out from the first diagnosis of T2DM, self-monitoring of blood glucose levels on an agreed frequency and appropriate use of a diabetes diary are simple but effective methods of diabetes monitoring (IDF, 2012). Furthermore, as there is an increased risk of death in T2DM patients during hypoglycaemic events (Bonds et al., 2010), educating patients about what to do when medication side effects occur is of great importance. The delegation of care to a diabetes nurse specialist, who can assist with patient self-management, is an established practice in Australia (Diabetes Australia, 2013).

4. Management Issues and Proposed Solutions

Management of ALD and T2DM should ideally involve input from not only clinicians, but also the patients themselves, the government and wider society. As will be discussed below, there is also a great need to employ a variety of strategies.

Alcohol Abstinence:

Though fundamental in preventing the progression of ALD, alcohol abstinence continues to be a challenge for ALD patients with many having a long history of dependence (Friedman., 2013).

Moreover, there are several socio-cultural factors that influence alcohol consumption, in turn affecting the management of alcohol-induced disorders. In Australian culture, alcohol represents a pivotal stepping stone to adulthood and is an essential part of celebrating meaningful events (Lindsay. et al., 2009). Furthermore, alcohol promotion and marketing strategies can influence patterns of alcohol use, especially in youth (Lindsay. et al., 2009). These include alcohol advertisements on free-to-air television, the use of print media, and the use of product placement in films and television (Wilson., Munro., Hedwards., & Cameron., 2012). Blurring the line between promotion and entertainment, alcohol companies expose the population with their products whilst subconsciously weaving their influence into our psyche. Therefore, it is important to consider the role of societal norms and the influence of the media in addressing ALD at a population level.

Unlike tobacco advertising which is subject to legislative prohibitions, there are no legislative alcohol equivalents. Instead, voluntary regulations have been created by the Alcohol Beverages Advertising Code Scheme but its uptake has been far from exemplary (The ABAC Scheme Limited, 2012); possibly, due to its establishment being funded and manned entirely by representatives from the alcohol industry (Sandra C & Gordon., 2013). As statutory regulations have been found the be the most effective policy measures in reducing the exposure of young people to advertising (Vendrame&Pinsky, 2011), independent and tighter regulations should be established to control advertising of alcoholic products.

Lifestyle modifications:

Several issues can affect the successful implementation of lifestyle modification, an important aspect of T2DM and ALD management. Despite its clear benefit, maintenance of substantial weight loss is only achieved by a small percentage of T2DM patients (Henry, Scheaffer, &Olefsky, 1985; Niskanen., Uusitupa., Sarlund., Siitonen., & Pyorala., 1990; Norris et al., 2004). This is important as the improvement in glycemic control that comes with dietary modification lasts only if the negative calorie balance and weight reduction are maintained (McCulloch, 2013). Challenges for patients arise from difficulties in adhering to a calorie-limited diet and the lowering of basal metabolic rate that can come with initial weight loss (McCulloch, 2013).

A key factor that hence needs to be addressed is the successful implementation of current initiatives in improving patients' capacity to self-manage, and to adhere to appropriate lifestyle changes. This is particularly important in T2DM as patients are largely responsible for the routine activities required to maintain glycaemic control (Hermanns et al., 2013). Often a source of significant stress for many (Surwit et al., 2002), it is thus important to move from a health professional-centred approach, which can contribute to lack of adherence (Griffin, 1999) to a more patient-focused approach. Furthermore, it is well-known that a multidisciplinary approach often leads to successful chronic disease intervention (Wagner, 1998; Wagner, Austin, & Von Korff, 1996); this is often limited however, by the availability of allied health services, amongst others (Comino et al., 2006). This can be improved through the establishment of multidisciplinary primary health services in which health professionals of various disciplines work together under one roof (Harris, Chan, & Dennis, 2009; Harris &Zwar, 2007), with several studies showing that patients who are looked after by a multidisciplinary team in one location have improved management of their chronic condition (Hogg et al., 2009) and health outcomes (Maislos& Weisman, 2004; Yu & Beresford, 2010). As such, doctors need to ensure proper treatment as opposed to ineffective transfer of care, coordinating clinicians and allied health professionals alike.

Liver transplantation:

Despite the significant health benefits of a liver transplant, a few issues need to be addressed. Firstly, many candidates who are alcohol dependent struggle to fulfil the pre- and post-transplant requirements of alcohol abstinence. Moreover, as T2DM leads to an increased risk of coronary artery disease (CAD), one must consider ALD patients who have co-morbid T2DM as the combination of CAD and T2DM leads to a poor prognosis after liver transplantation (Ripoll, Yotti, Bermejo, &Banares, 2011). Despite this, there is no standardisation of management of CAD available in the pre-transplant period (Ripoll et al., 2011). Aggressive primary prevention through early recognition of risk factors and health promotion, is thus of the utmost importance, alongside addressing the psychosocial elements of alcohol dependence, as outlined previously. Post-liver transplantation, T2DM and CAD must be continued to be treated aggressively.

Glucocorticoids and pentoxifylline:

Glucocorticoids are used in the management of ALD. However, in patients with concurrent T2DM, they may be relatively contraindicated as they can exacerbate blood glucose levels (Saag. &Furst., 2013) and, in patients with subclinical diabetes, can precipitate new-onset hyperglycemia (M ukamal., 2013). As such the use of pentoxifylline (a TNF antagonist) has been proposed as an alternative. However, while Akriviadis et al. (2000) touts its survival benefit when compared to placebo (76% vs. 54%), Massart et al.(2012) report that based on murine models, pentoxifylline administration may have the potential to aggravate pre-existing T2DM in patients. Evidently, further research into its effects will need to be carried out.

The role of medical students

While medical students do not individually possess much power, collectively they are capable of achieving much more. There are several m edical student organizations across Australia and most of them are dedicated to promoting health to the general population. For example, Hepatitis B Free Australia is a student run organization dedicated to promoting public awareness of the silent epidemic

Conclusion

Currently, there is good evidence to suggest that the metabolic effects of T2DM have a detrimental effect on liver function. Similarly, the r ole of alcohol in the development of hepatocellular dysfunction in ALD has been well-elucidated in the current literature. However, as reflected in th e results of our literature review, there is much less information regarding the effects of these two conditions on liver function when they occur toge ther. We conclude that this is a notable gap in the literature regarding the topic, and is of significant importance given the potential of worse liver o utcomes occurring in these patients in the face of epidemics of both conditions in Australia. As such, further research in the area needs to occur in order to develop well-defined strategies to prevent and manage the combined effects of T2DM and ALD should they occur concurrently.

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Figures

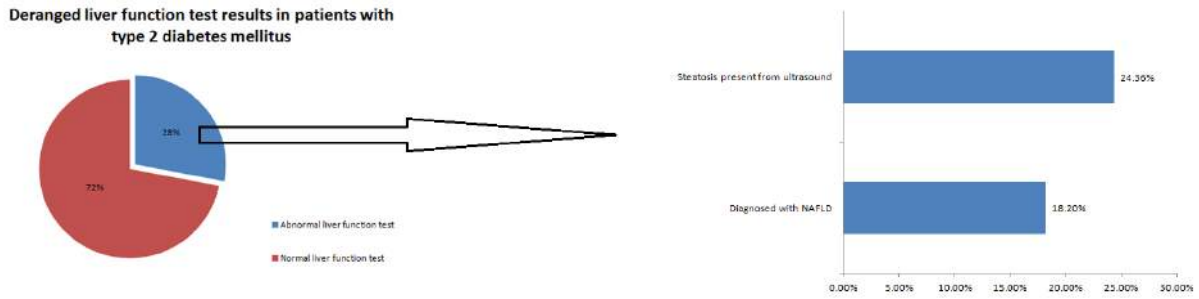

Figure 1. LFT derangement in asymptomatic T2DM

Figure 2. Inadvertent diagnosis of NAFLD and steatosis in asymptomatic T2DM

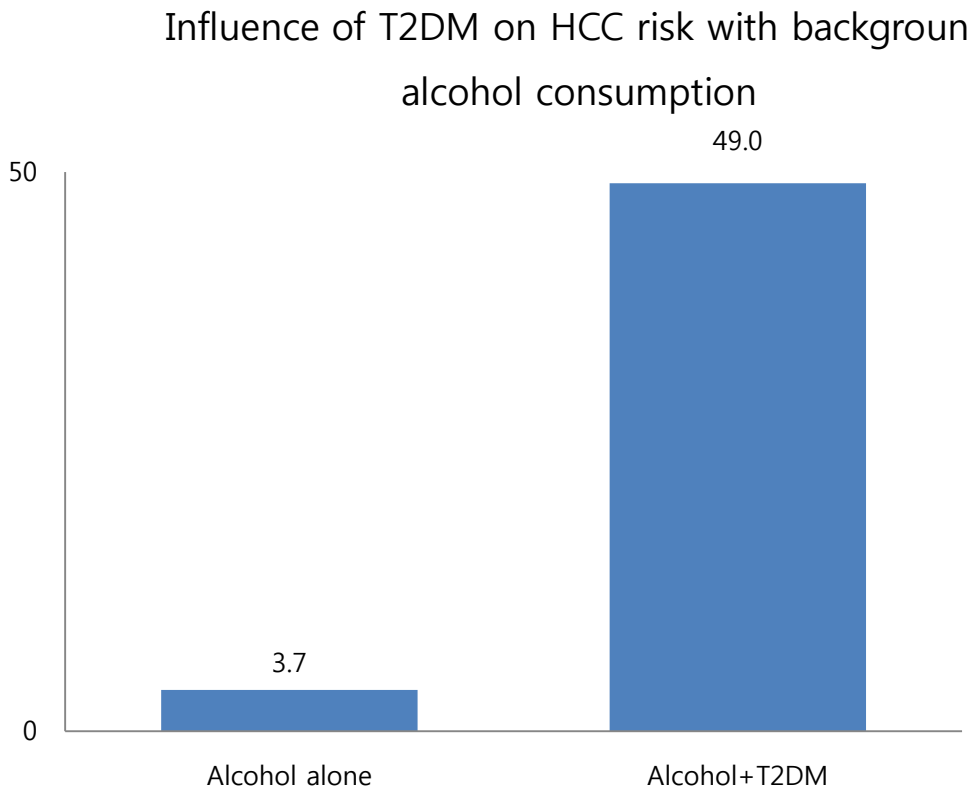

Figure 3. Influence of T2DM on HCC risk with Background Alcohol Consumption

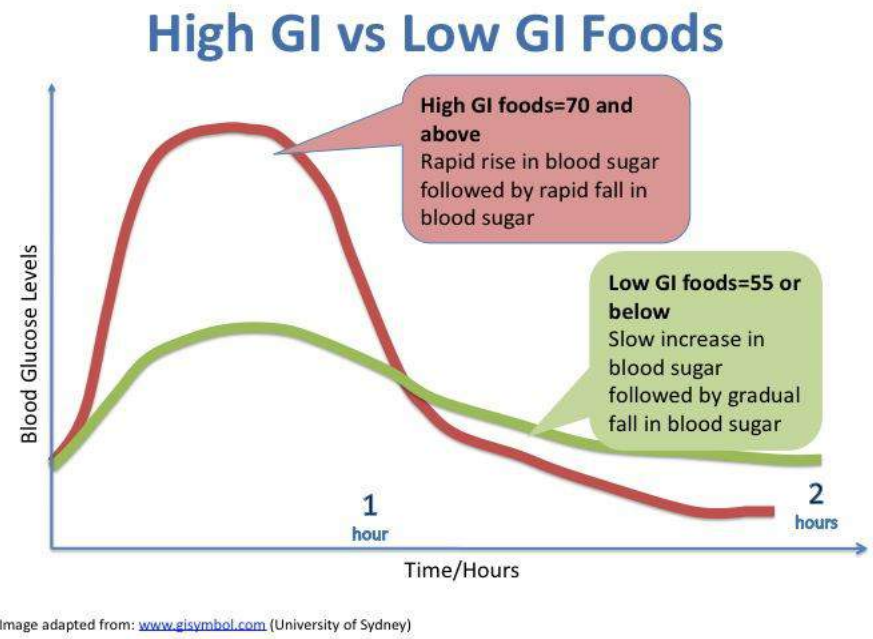

Figure 4. Blood Glucose Levels in High vs. Low GI Foods. Taken from MJA (online).

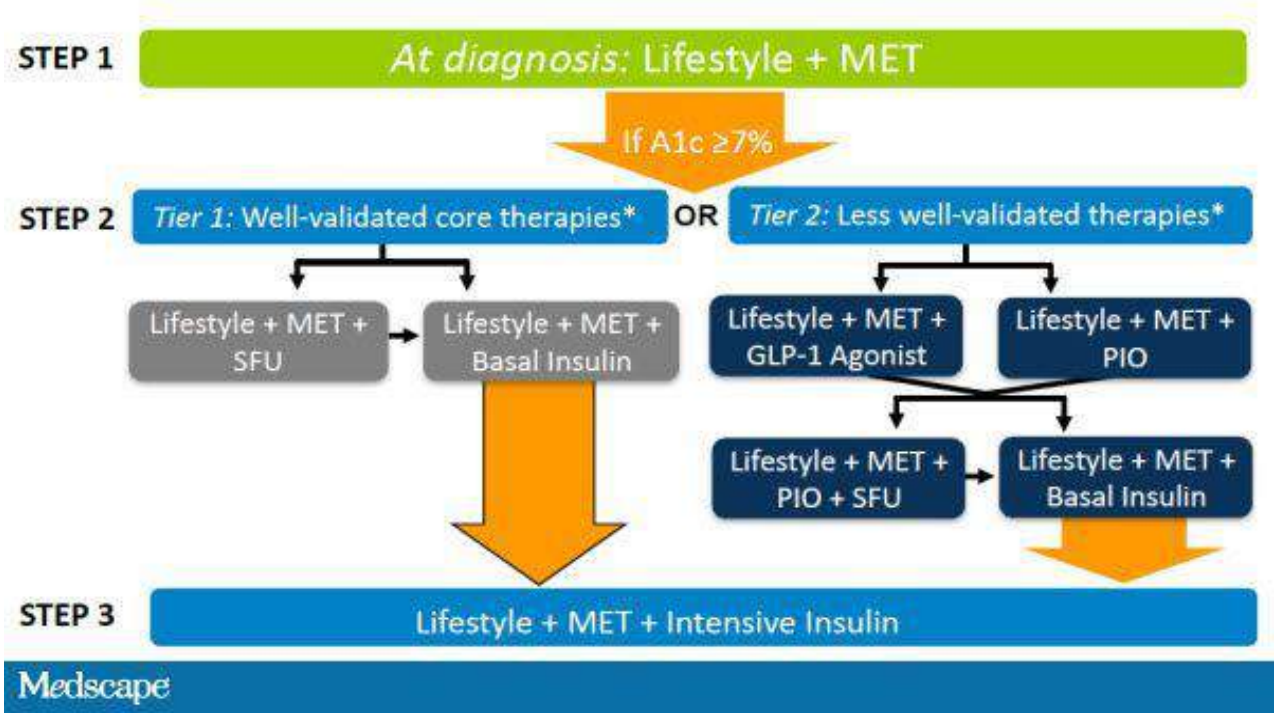

Figure 5. Common Treatment Pathway for Glycaemic Control of T2DM Patients in Australia. Taken from Medscape (online).

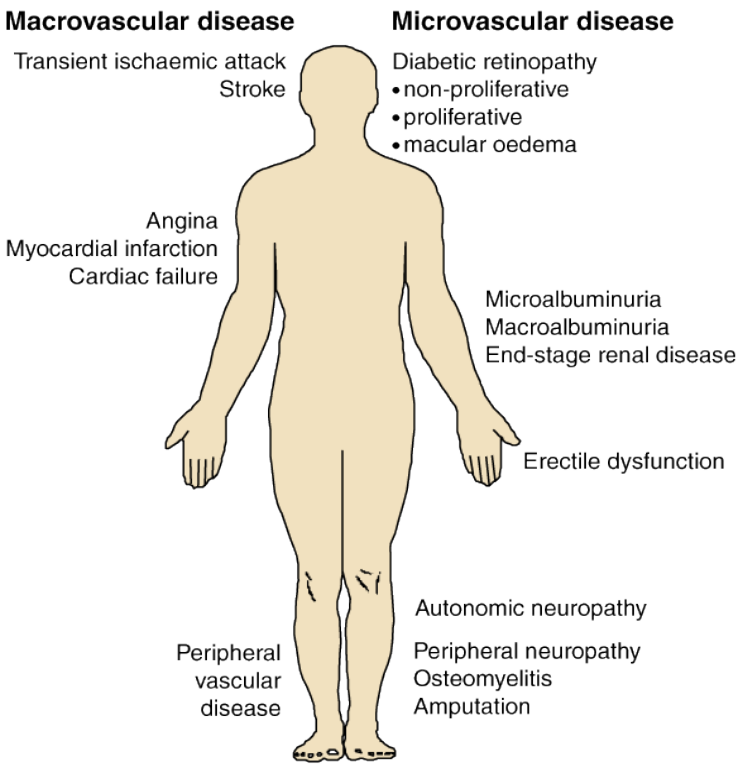

Figure 6. Diabetes Complications – Microvascular and Macrovascular Disease. Taken from MJA (online).

The association between the gene polymorphisms and nasopharyngeal carcinoma risk: evidence from comprehensive meta-analyses

China

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Abstract

Background: Nasopharyngeal carcinoma is a malignant tumor of the nasopharynx that has a strong geographical distribution with a high incidence in Southern China The gene polymorphisms have been implicated in susceptibility of nasopharyngeal carcinoma, but studies have reported inconclusive results. The present study investigated the relationship between the gene polymorphisms and risk of nasopharyngeal carcinoma by meta-analysis.

Method: Data from Pubmed, CNKI, Wanfang, and Weipu databases was evaluated and analyzed. Statistical analysis was performed by using the software Revman4.2 and STATA 10.0.

Results: A total of 9707 nasopharyngeal carcinoma cases and 11041 controls in 34 case-control studies were identified for data analysis. The results suggested that the -1306C> T polymorphism of *MMP-2* gene (OR=0.58, 95%CI=0.46-0.74, P<0.0001) and the Arg72Pro polymorphism of *p53* gene (OR=0.67, 95%CI=0.46-0.98, P=0.04) might be related to decreased risks of nasopharyngeal carcinoma, while the detected polymorphisms in *XRCC1, MDM2, MMP-1* and *CYP2E1* genes might not contribute to the risk of nasopharyngeal carcinoma.

Conclusions: This current meta-analysis suggested that the -1306C> T polymorphism of *MMP-2* gene and the Arg72Pro polymorphism of *p53* gene might be protective factors of nasopharyngeal carcinoma . Future studies are needed to validate our findings.

Keywords: risk, polymorphism, nasopharyngeal carcinoma, meta-analysis

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Introduction

Current epidemiology of nasopharyngeal carcinoma in china and the world

Nasopharyngeal carcinoma is a malignant tumor of the nasopharynx that has a strong geographical distribution, with a high incidence in Southern China, while r are in most parts of the world (Fig. 1). Globally, there are the very populations of which the incidence is notably higher, Southeast Asian (southern China, Thailand, Philippin es and Vietnam), North Africans (Algeria, Morocco) and the arctic region (Canada and Alaska)(Barnes, 2005). An investigative report made by WHO shows that 80% patients with nasopharyngeal carcinoma live in China(Guangdong, Guangxi, Hunan)(B, 2013). The incidence is 30/105-50/105 in south of China, while 2/105-3/105 in the North of Chi na. Nasopharyngeal carcinoma occurs in children and adults. Nasopharyngeal carcinoma incidence rises after the age of 20 and peaks at 55-59 years old (10.09/105) and de clines after 60 years old (3.65/105 after 85 years old) (B, 2013). The age distribution is similar in males and females, although rates in male are higher than those in female (such as 55 -59 years old male 14.07/105, female 6.04/105)(B, 2013).

Pathologic basis of nasopharyngeal carcinoma

Nasopharyngeal carcinoma arises from the mucosal epithelium of the nasopharynx. In the third edition of 2003 WHO classification, three histological types of na sopharyngeal carcinoma encompass keratinizing squamous cell carcinoma, nonkeratinizing squamous cell carcinoma (differentiated, undifferentiated), and basalold squamou s cell carcinoma. nonkeratinizing undifferentiated form also known as lymphoepithelioma is most common.

Management of nasopharyngeal carcinoma in china

The clinical symptoms of nasopharyngeal carcinoma include nose bleeding, nasal obstruction, tinnitus, headache, cervical lymph nodes enlargement, cranial nerv e lesions and distant metastasis. Nasopharyngeal carcinoma can be diagnosed through imageological examination such as X-ray, MRI, CT, PET-CT and biopsy. The treatmen t of nasopharyngeal carcinoma is based on radiation therapy, chemotherapy, surgery, biological agents and targeted therapy, according to staging systems for nasopharyng eal carcinoma. The most common used staging system is the "tumor node metastasis (TNM)" system, jointly developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) (Fig. 2,3)(Pan et al., 2013). Nasopharyngeal carcinoma is highly sensitive to radiation. Radiation therapy is the main th e treatment for nasopharyngeal carcinoma with no distant metastasis and concurrent chemoradiothrapy (CCRT) was more beneficial compared with radiation therapy alone in locoregionally advanced nasopharyngeal carcinoma patients(X, 2013).

Avoiding contact with risk factors is the main precautions. Smoking cessation, light-based diet and avoiding adverse exposure are the effective ways to decrea se the risk of nasopharyngeal carcinoma.

Risk factors of nasopharyngeal carcinoma

The risk factors in diseases causation include genetic susceptibility, environment factors and infection by Epstein-Barr virus(Barnes, 2005). The specific geographic al and demographic distribution of nasopharyngeal carcinoma reflects the genetic susceptibility. Apart from genetic factor, there is much evidence showing that infection b y EBV is a probable oncogenic factor in the genesis of nasopharyngeal carcinoma. Environmental factors include Diet, such as high-salt food, cigarette smoking, occupation al exposure to smoke, chemical fumes and dusts formaldehyde exposure, and radiation exposure.

Up to now, the associations between the gene polymorphisms and the risks of nasopharyngeal carcinoma have been broadly studied. However, the results were inconclusive. Therefore, in order to overcome the limitations of individual studies, we performed this meta-analysis. This is, to our knowledge, the most comprehensive serie s of meta-analyses in respect of the gene polymorphism and nasopharyngeal carcinoma risk.

Methods and materials

Study identification and selection

A systematic search of literature was performed to investigate the associations between the gene polymorphisms and nasopharyngeal carcinoma risk. Pubmed, C NKI (National Knowledge Infrastructure), WanFang, and Weipu databases were used (the last search was performed on Oct. 28th, 2013). The search terms were *nasopharyng eal carcinoma* in combination with *polymorphism* or *variant* or *mutation.* There was no limitation to language. The inclusion criteria were as follows: (a) studies evaluating th e association between the gene polymorphisms and nasopharyngeal carcinoma risk; (b) case-control studies designed with nasopharyngeal carcinoma participants and healt hy participants, (c) studies with sufficient data (genotype distributions of cases and controls) available to calculate an OR (odds ratio) with its 95%CI (confidence interval), (d) genotype distributions of control population must be consistent with Hardy–Weinberg equilibrium (HWE). The following exclusion criteria were used: (a) studies based on fa mily or sibling pairs, (b) studies with genotype frequencies or numbers not presented, (c) case reports, reviews or conference abstracts. If more than one case-control studie s were published by the same authors using the same case series or overlapped case series, studies with the largest sample size or the newest were included.

Data extraction

Two reviewers independently extracted the data and reached a consensus on all items. The following information was extracted from each study: author, publicat ion year, country of origin, ethnicity, genotype number in cases and controls.

Statistical analysis

The strength of the association between the gene polymorphisms and nasopharyngeal carcinoma risk was measured by ORs and 95% CI. The statistical significan ce of summary OR was determined with Z-test. The genetic models used for data analysis for the polymorphism were dominant model: VV+VW vs. WW, recessive model: V V vs. VW+WW and other genetic models: VV vs. WW, VW vs. WW and V vs. W (VV=variant homozygote, VW= heterozygote, WW= wild homozygote, V=variant type, W=wil d type). The heterogeneity was assessed by a X^2 based Q statistic and was considered statistical significant at P <0.10. The pooled OR was analyzed by a fixed-effects mode l (the Mantel-Haenszel method) or a random-effects model (the DerSimonian and Laird method) according to the heterogeneity. When the P value was > 0.10, the pooled OR was calculated by the fixed-effects model, otherwise, the random-effects model was used.

Publication bias was analyzed by visual inspection of asymmetry in funnel plots and the Begg's test and Egger's test were also carried out for statistical assessme nt. Sensitivity analysis was conducted by sequentially deleting a single study each time in an attempt to identify the potential influence of the individual data set to the poo led ORs. All statistical tests were performed by RevMan 4.2 and Stata 10.0 software(Y. G. Zhang et al., 2011).

Results

Study Selection and Characteristics

Figure 4 shows the studies selection process. Briefly, a total of 1621 results were identified after an initial search from the Pubmed, CNKI, Wanfang and Weipu da tabases. After reading the titles and abstracts, 1452 results were excluded for being not relevant to gene polymorphisms and risk of nasopharyngeal carcinoma After readin g full-texts of the remaining 169 studies, 68 studies were excluded for published as abstracts, reviews and duplicated results. Thus, 101 studies were left for data extraction. A total of 87 case-controls were extracted for these three polymorphisms. Among 87 case-control studies, genotype numbers for control group in 7 studies were not consis tent with HWE; data in 19 studies were overlapped. So these 26 case-control studies were excluded. In addition, polymorphisms with less than three original studies were el iminated. Finally, a total of 75 case-control studies in 74 studies were identified for meta-analysis. Summary of the properties of the studies are listed in Table 1. Overall, the re were 5 case-controls studies on the Arg399Gln polymorphism of *XRCC1* (X-ray repair cross-complementing protein 1) gene(Cao et al., 2006; Cho et al., 2003; Laantri et al. , 2011; Q. Li et al., 2013; Qiong, li, & hui, 2007), 4 case-control studies on the Arg194Trp polymorphism of *XRCC1* gene(Cao et al., 2006; Laantri et al., 2011; Qiong et al., 200 7; Yang et al., 2007), 4 case-control studies on the Arg280His polymorphism of *XRCC1* gene(Cho et al., 2003; Laantri et al., 2011; Qiong et al., 2007; Yang et al., 2007), 3 case -control studies on the 309T> G polymorphism of *MDM2* (Mouse double minute 2 homolog) gene(Sousa, Pando, Breda, Catarino, & Medeiros, 2011; Xiao et al., 2010; X. Zh ang, 2008), 4 case-control studies on the 1G/2G polymorphism of *MMP-1* (Matrix metalloproteinase-1) gene(Kondo et al., 2005; Wei et al., 2010; Zhou et al., 2007), 3 case-c ontrol studies on the -1306C> T polymorphism of *MMP-2* (matrix metalloproteinase-2) gene(Shao et al., 2011; Zhou et al., 2007), 3 case-control studies on the RsaI polymor phism of *CYP2E1* (Cytochrome P450 2E1) gene (He et al., 1999; Hildesheim et al., 1997; Hildesheim et al., 1995) and 8 case-control studies on the Arg72Pro polymorphism of *p53* (protein 53) gene(L. Li et al., 2013; Santos et al., 2006; Tiwawech, Srivatanakul, Karaluk, & Ishida, 2003; Tsai et al., 2002; Xiao et al., 2010; Yoon et al., 2008; Yung, Ng, Sha m, & Choy, 1997; X. Zhang, 2008). The genotype occurrences for the polymorphisms above are also listed in Table 1.

Quantitative data synthesis

XRCC1 gene

A total of 13 case-control studies were included in the meta-analysis on the relationship between the Arg399Gln, Arg194Trp and Arg280His polymorphisms of *X RCC1* gene and the risk of nasopharyngeal carcinoma. No statistical significant results were found in dominant model. Four other genetic models were also used and the su mmary of the results of genetic comparisons are listed in Table 2.The results suggested that individuals with Arg399Gln polymorphisms might have an increased nasophary ngeal carcinoma risk under the Gln/Gln vs. Arg/Arg genetic comparison model.

MDM2 gene

A total of 1126 cases and 1801 controls were included in the meta-analysis on the relationship between the 309T> G gene polymorphisms and the risk of nasop haryngeal carcinoma. Overall, OR was 1.13(95%CI=0.61-2.10) and the test for overall effect Z value was 0.39 (P=0.70) for TG+GG vs. TT model. Four other genetic models we re also used and the summary of the results of genetic comparisons are listed in Table 2.The results suggested that individuals who carry G allele (TG+GG) may not have an increased/decreased nasopharyngeal carcinoma risk compared with the homozygote TT carriers.

MMP-1 gene

A total of 936 cases and 1113 controls were included in the meta-analysis on the relationship between the 1G/2G gene polymorphisms and the risk of nasophar yngeal carcinoma. Overall, OR was 0.90(95%CI=0.20-4.10) and the test for overall effect Z value was 0.14 (P=0.89) for G1G1+G1G2 vs. G2G2 model. Four other genetic mode ls were also used and the summary of the results of genetic comparisons are listed in Table 2.The results suggested that individuals who carry G2 allele (G1G1+G1G2) may not have an increased/decreased nasopharyngeal carcinoma risk compared with the homozygote G2G2 carriers.

MMP-2 gene

A total of 1173 cases and 1149 controls were included in the meta-analysis on the relationship between the -1306C> T gene polymorphisms and the risk of naso pharyngeal carcinoma. The heterogeneity of CT+TT vs. CC for all 3 case-control studies was analyzed. The value of X^2 was 1.59 with 2 degrees of freedom in a fixed-effect model. Additionally, I^2 value is another index of the test of heterogeneity. The I^2 was 0%, suggesting the absent of heterogeneity. Thus, the random-effect model was chose n to synthesize the data. Overall, OR was 0.59(95%CI=0.46-0.74) and the test for overall effect Z value was 4.34 (P< 0.0001) for CT+TT vs. CC model (Fig 5). Four other genet ic models were also used and the summary of the results of genetic comparisons are listed in Table 2.The results suggested that the -1306C> T polymorphism may be a pr otective factor of nasopharyngeal carcinoma.

CYP2E1 gene

A total of 517 cases and 463 controls were included in the meta-analysis on the relationship between the RsaI polymorphisms and the risk of nasopharyngeal ca rcinoma. Overall, OR was 0.65(95%CI=0.73-1.22) and the test for overall effect Z value was 0.46 (P=0.65) for dominant model. Four other genetic models were also used and the summary of the results of genetic comparisons are listed in Table 2. The results suggested that individuals with RsaI polymorphisms might have an increased nasophary ngeal carcinoma risk under the C2C2 vs. C1C2+C1C1 and C2C2 vs. C1C1genetic comparison model.

p53 gene

A total of 1699 cases and 2155 controls were included in the meta-analysis on the relationship between the Arg72Pro gene polymorphisms and the risk of nasop haryngeal carcinoma. The heterogeneity of ArgArg+ ProArg vs. Pro Pro for all 8 case-control studies was analyzed. The value of X^2 was 26.42 with 7 degrees of freedom in a random-effect model. Additionally, I^2 value is another index of the test of heterogeneity. The I^2 was 73.5%, suggesting the present of heterogeneity. Thus, the random-effec t model was chosen to synthesize the data. Overall, OR was 0.67(95%CI=0.46-0.98) and the test for overall effect Z value was 2.06 (P=0.04) for ArgArg+ ProArg vs. Pro Pro model (Fig 6). Four other genetic models were also used and the summary of the results of genetic comparisons are listed in Table 2. The results suggested that the Arg72 Pro polymorphism may be a protective factor of nasopharyngeal carcinoma.

Publication bias

Publication bias was assessed by Begg's funnel plot and Egger's test. The shape of the funnel plots seemed symmetrical in the dominant comparison genetic mo del, suggesting the absence of publication bias. Then, the Egger's test was performed to provide statistical evidence of funnel plot asymmetry (Figure not shown). The result s indicated a lack of publication bias of the current meta-analysis.

Sensitivity analysis

In order to assess the stability of the results of the current meta-analysis, we performed a one-study removed sensitivity analysis for dominant genetic model. St atistically similar results were obtained after sequentially excluding each study, suggesting the stability of our meta-analysis in general.

Discussion

Individual susceptibility to nasopharyngeal carcinoma varies with not only environmental exposures but also genetic background. The gene polymorphisms have been reported to be associated with the risk of nasopharyngeal carcinoma but the results remains inconclusive. The current meta-analysis, including a total 9707 nasopharyngeal carcinoma cases and 11041 controls in 34 case-control studies, investigated the association between the gene polymorphisms and nasopharyngeal carcinoma risk. Our results indicated that the -1306C> T polymorphism of *MMP-2* gene and the Arg72Pro polymorphism of *p53* gene might be related to decreased risks of nasopharyngeal carcinoma. However, the Arg399Gln, Arg194Trp and Arg280His polymorphisms of *XRCC1* gene, the 309T> G polymorphism of *MDM2* gene, the 1G/2G polymorphism of *MMP-1* gene and the RsaI polymorphism of *CYP2E1* gene might not contribute to the risk of nasopharyngeal carcinoma. These outcomes further indicated the complexity of pathogenesis of d nasopharyngeal carcinoma and the related complications. In addition, the correlation of gene, ethnicity, environment and other factors may potentially influence the diseases.

The methodological issues for the present meta-analysis were all well investigated. There was controllable heterogeneity found in analyses with any genetic model. No publication bias was detected although there was still potential omitted data such as that from conference abstracts. The sensitivity analysis indicated that the data in a single publication may have a significant influence on the overall result. In general, stability and accuracy of the present meta-analysis were guaranteed.

Some limitations of this meta-analysis should be considered. First, case-control studies were from Caucasians and Asian, so our results could only be applicable to these two ethnic groups only. Future studies are needed to investigate the association in other populations. Second, only studies included by the selected databases were included for data analysis and some relevant published studies or unpublished studies with null results might be missed, which may also bias our results. Despite the limitations, we have minimized the bias through the whole process based on means in study identification, data selection and statistical analysis as well as in the control of publication bias and sensitivity, the result is reliable.

In conclusion, this study is the first meta-analysis to date to have assessed the association between the gene polymorphisms and nasopharyngeal carcinoma risk. Our results suggested that the -1306C> T polymorphism of *MMP-2* gene and the Arg72Pro polymorphism of *p53* may be associated with a decreased nasopharyngeal carcinoma risk. Still, future large-scale case-control studies are needed to validate these conclusions.

Conclusion

The -1306C> T polymorphism of *MMP-2* gene and the Arg72Pro polymorphism of *p53* gene might be protective factors of nasopharyngeal carcinoma .

Conflict of Interest

The authors declare that they have no competing interests.

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Figures and Tables

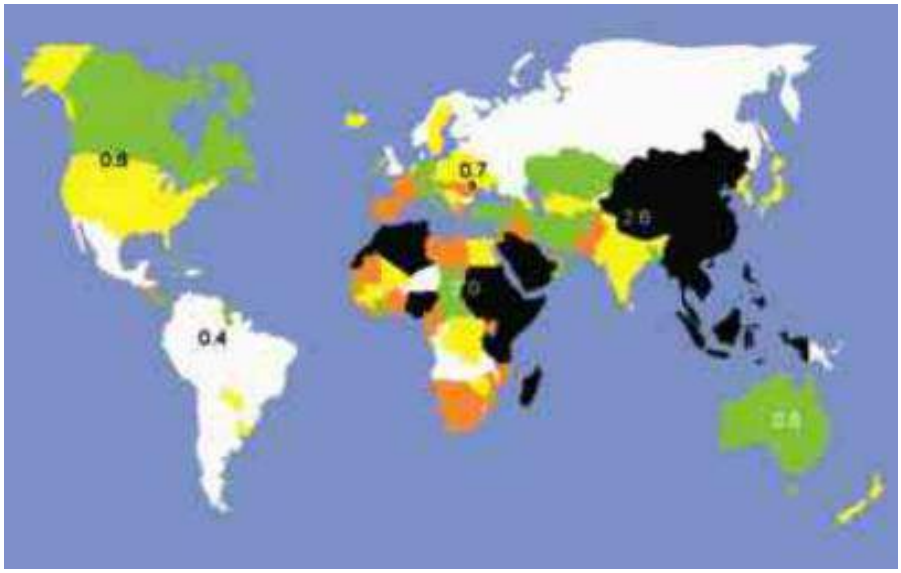


Figure1.

T-primary tumor

T1 Nasopharynx, oropharynx, or nasal cavity extension

T2 Parapharyngeal extension

T3 Bony structure, paranasal sinuses extension

T4 Intracranial extension, cranial nerve, hypopharynx, orbit, infratemporal fossa (masticatory space) extension

N-regional lymph nodes

N0 No regional lymph node metastasis

N1 Unilateral metastasis in lymph node(s), uni/bilateral retropharyngeal lymph node, r6cm in greatest dimension, above the supraclavicular fossa

N2 Unilateral metastasis in lymph node(s), r6cm in greatest dimension, above the supraclavicular fossa involvement

N3a >6cm in greatest dimension

N3b Extension to the supraclavicular fossa

M-distant metastasis

M0 No distant metastasis

M1 Distant metastasis

Stage grouping

Stage I: T1 N0 M0

Stage II: T1 N1 M0, T2 N0-1 M0

Stage III: T1-2 N2 M0 ,T3N0-2 M0

Stage IVa: T4 N0-2 M0

Stage IVb: Any T N3 M0

Stage IVc: Any T Any N M1

Figure2.

T-primary tumor

T1 Tumor confined to nasopharynx

T2 Nasal cavity, oropharynx, parapharyngeal extension

T3 Skull base, medial pterygoid muscle extension

T4 Cranial nerve, paranasal sinus, masticatory space excluding medial pterygoid muscle, intracranial (cavenous, dural meninges) extension

N-regional lymph nodes

N0 No regional lymph node metastasis

N1a Retropharyngeal lymph node involvement

N1b Unilateral level Ib, II, III, and Va involvement, and the maximum diameter 3cm

N2 Bilateral level Ib, II, III, and Va or the maximum diameter >3cm or with extranodal neoplastic spread

N3 Level IV, Vb involvement

M-distant metastasis

M0 No distant metastasis

M1 Distant metastasis

Stage grouping

Stage I: T1 N0 M0

Stage II: T1 N1a-1b M0,T2 N0-1b M0

Stage III: T1-2 N2 M0, T3 N0-2 M0

Stage IVa: T1-3 N3 M0, T4 N0-3 M0

Stage IVb: Any T Any N M1

Figure3.

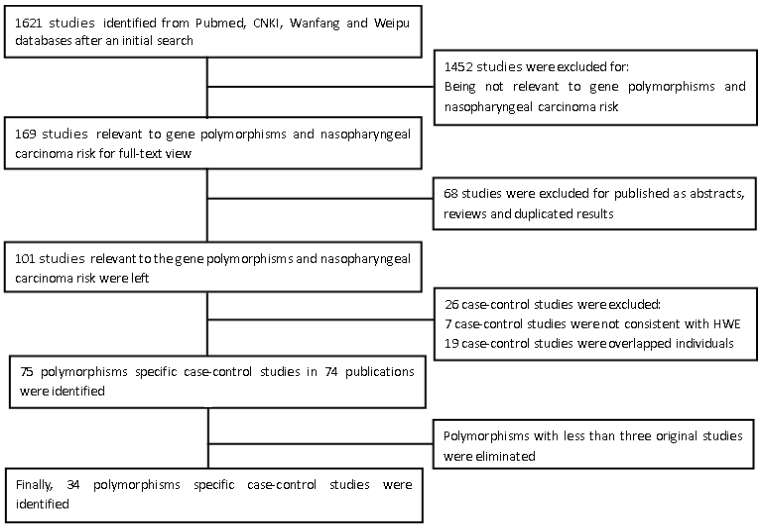
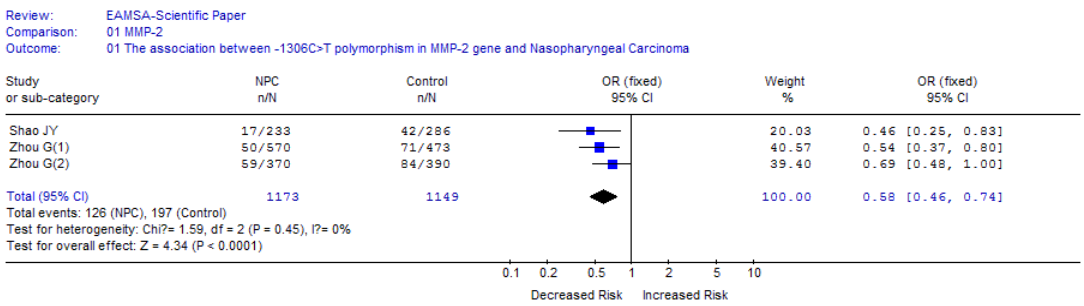


Figure4.



Figur5.

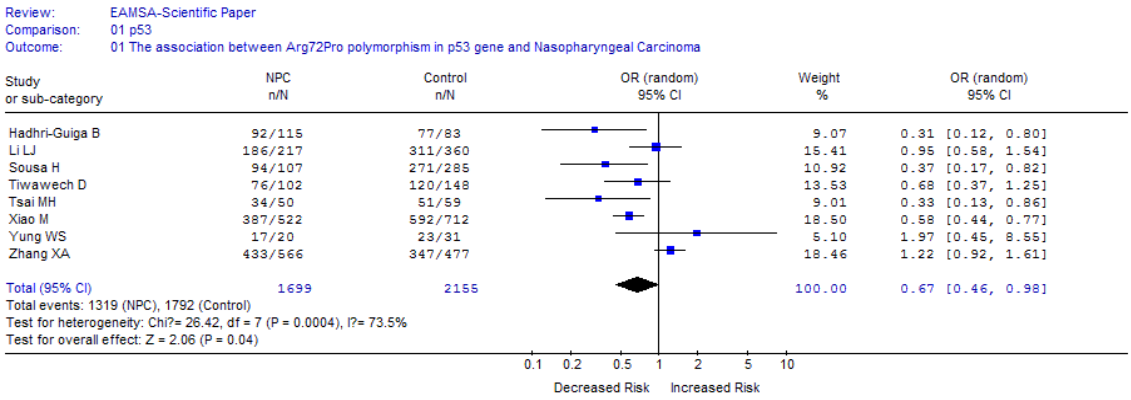


Figure6.

Table 1. Characteristics of publications included and distribution ofgenotypes and alleles among nasopharyngeal carcinoma patients and controls

Author	Year	Country	Ethnicity	Case			Control			HWE
The Arg399Gln polymorphism of XRCC1 gene				Arg/Arg	Arg/Gln	Gln/Gln	Arg/Arg	Arg/Gln	Gln/Gln	
Cao Y	2006	China	Asian	241	152	32	270	201	30	Yes
Cho EY	2003	China	Asian	174	128	32	152	109	21	Yes
Dai Q	2007	China	Asian	93	54	6	95	67	6	Yes
Laantri N	2011	China	Asian	274	193	45	279	163	35	Yes
Li Q	2013	China	Asian	92	117	22	166	114	20	Yes
The Arg194Trp polymorphism of XRCC1 gene				Arg/Arg	Arg/Trp	Trp/Trp	Arg/Arg	Arg/Trp	Trp/Trp	
Cao Y	2006	China	Asian	232	166	19	235	217	43	Yes
Dai Q	2007	China	Asian	116	91	13	168	73	9	Yes
Laantri N	2011	China	Asian	492	55	4	470	41	1	Yes
Yang ZH	2007	China	Asian	62	79	12	99	65	4	Yes
The Arg280His polymorphism of XRCC1 gene				Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His	
Cho EY	2003	China	Asian	275	55	2	215	66	2	Yes
Dai Q	2007	China	Asian	173	43	4	209	37	4	Yes
Laantri N	2011	China	Asian	431	114	10	405	92	9	Yes
Yang ZH	2007	China	Asian	125	27	1	131	35	2	Yes
The 309T > G polymorphism of MDM2 gene				TT	TG	GG	TT	TG	GG	
Sousa H	2011	Portugal	European	51	52	23	217	244	48	Yes
Xiao M	2010	China	Asian	111	243	168	238	346	128	Yes
Zhang X	2008	China	Asian	120	220	138	111	276	193	Yes
The 1G/2G polymorphism of MMP-1 gene				2G2G	1G2G	1G1G	2G2G	1G2G	1G1G	
Gao W	2010	China	Asian	103	100	38	52	121	99	Yes
Kondo S	2005	Japan	Asian	41	32	10	19	44	19	Yes
Zhou(1)	2007	China	Asian	24	285	65	183	235	61	Yes
Zhou(2)	2007	China	Asian	113	96	29	110	132	38	Yes
The -1306C > T polymorphism of MMP-2 gene				CC	CT	TT	CC	CT	TT	
Shao JY	2011	China	Asian	311	59	0	306	83	1	Yes
Zhou G(1)	2007	China	Asian	216	17	0	244	42	0	Yes
Zhou G(2)	2007	China	Asian	520	50	0	402	70	1	Yes
The RsaI polymorphism of CYP2E1 gene				C1C1	C1C2	C2C2	C1C1	C1C2	C2C2	
He ZM	1999	China	Asian	72	27	6	59	33	1	Yes
Hildesheim A(1)	1997	China	Asian	229	108	27	198	113	9	Yes
Hildesheim A(2)	1995	China	Asian	30	11	7	33	16	1	Yes
The Arg72Pro polymorphism of p53 gene				ProPro	ProArg	ArgArg	ProPro	ProArg	ArgArg	
Hadhri-Guiga B	2007	Tunisia	Caucasian	23	48	44	6	45	32	Yes
Li LJ	2013	China	Asian	31	113	73	49	186	125	Yes
Sousa H	2006	Portugal	Caucasian	13	32	62	14	93	178	Yes
Tiwawech D	2003	Thailand	Asian	26	52	24	28	70	50	Yes
Tsai MH	2002	China	Asian	16	14	20	8	26	25	Yes
Xiao M	2010	China	Asian	135	270	117	120	366	226	Yes
Yung WS	1997	China	Asian	3	11	6	8	13	10	Yes
Zhang XA	2008	China	Asian	133	292	141	130	229	118	Yes

Table 2. Comparison results of the total and subgroup analyses of the gene polymorphisms in different genetic models

Gene	SNP	n[a]	VV+VW *vs.* WW[b]		VV *vs.*VW+WW[b]		VV *vs.*WW[b]		VW *vs.*WW[b]		V *vs.*W[b]	
			OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p
XRCC1	Arg399Gln	5	1.14(0.88,2.47)	0.33	1.29(0.99,1.67)	0.06	**1.35(1.04,1.77)**	**0.03**	1.10(0.84,1.45)	0.48	1.13(0.95,1.34)	0.16
	Arg194Trp	4	1.37(0.80,2.34)	0.25	1.53(0.53,4.41)	0.43	1.79(0.50,6.40)	0.37	1.34(0.84,2.14)	0.22	1.30(0.80,2.11)	0.28
	Arg280His	4	0.96(0.69,1.35)	0.83	0.97(0.49,1.91)	0.92	0.98(0.50,1.94)	0.96	0.97(0.69,1.37)	0.86	0.96(0.72,1.29)	0.81
MDM2	309T > G	3	1.13(0.61,2.10)	0.70	1.54(0.74,3.17)	0.25	1.55(0.57,4.20)	0.39	1.01(0.63,1.61)	0.96	1.20(0.73,1.98)	0.46
MMP-1	1G/2G	4	0.90(0.20,4.10)	0.89	0.67(0.31,1.44)	0.31	0.74(0.13,4.36)	0.74	0.99(0.22,4.35)	0.99	0.75(0.33,1.74)	0.51
MMP-2	-1306C > T	3	**0.58(0.46,0.74)**	**<0.0001**	0.31(0.03,3.00)	0.31	0.29(0.03,2.80)	0.29	**0.59(0.46,0.75)**	**<0.0001**	**0.60(0.48,0.76)**	**<0.0001**
CYP2E1	RsaI	3	0.94(0.73,1.22)	0.65	**3.47(1.76,6.83)**	**0.0003**	**3.22(1.62,6.38)**	**0.0008**	0.79(0.60,1.03)	0.09	1.13(0.91,1.40)	0.28
p53	Arg72Pro	8	**0.67(0.46,0.98)**	**0.04**	**0.81(0.70,0.93)**	**0.004**	**0.62(0.41,0.93)**	**0.02**	0.70(0.47,1.03)	0.07	**0.82(0.69,0.98)**	**0.03**

The bold values mean that their association is significant.

[a]Number of case-control studies

[b]VV=variant homozygote, VW= heterozygote, WW= wild homozygote, V=variant type, W=wild type

Scientific Paper Abstract – Hong Kong

The Role of Leisure Activities in Vascular Cognitive Impairment: Preliminary Findings from the Stroke Registry Investigating Cognitive Decline (STRIDE) Study

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Background

With an aging population crisis in Hong Kong, the increasing burden of age-dependent diseases on the healthcare system is in need of redress. Of particular concern is cognitive impairment caused by vascular diseases, such as stroke. Many studies demonstrated that a modification of lifestyle factors, inc reasing the utilization of cognitive abilities, may delay the onset of dementia. While a multitude of stu dies have looked at the effect of leisure activities as an interventional lifestyle factor post-stroke, ours is the first study to assess the effect of leisure activities both before and after stroke on the rate of cognit ive decline. We hypothesized that physical and non-physical leisure activities would function to slow d own cognitive decline after stroke, thus reducing the risk of developing post-stroke dementia.

Methods

Preliminary data was taken from the ongoing Stroke Registry Investigating Cognitive Decline (ST RIDE) study, which is a 5-year prospective cohort study that looks at cognitive decline after a stroke or t ransient ischemic attack (TIA) event. Patients recruited into the study were given a questionnaire at bas eline (3-6 months post-stroke) and at 15-18 months follow up regarding their tendency to engage in lei sure activities, including physical, intellectual, social and recreational activities. Cognitive function was a ssessed at the same time using three established neuropsychological tests (CDR, MoCA, MMSE).

Results

Physical, recreational or intellectual activities were found to be positively associated with cognitiv e function at baseline. At follow-up, patients who participated in any type of leisure activityperformed better in the neuropsychological tests in comparison to those who were inactive.

Conclusions

The effects of leisure activities is consistent with previous studies. Our study adds to the current l iterature thatboth pre-stroke and post-strokeleisure activity protects against post-stroke cognitive decli ne. This suggests that engaging in leisure activities can be used as an interventional treatment post-str oke and as protective mechanism pre-stroke to delay cognitive decline.

Preliminary findings from the STRIDE study highlighted the beneficial effects of leisure activities b efore and after stroke in slowing cognitive decline. Longer-term follow-up is warranted to completely a ssess the long-term prognosis of cognition and to elucidate the hazard ratio of VCI between those who do and do not actively engage in leisure activities.

The Role of Leisure Activities in Vascular Cognitive Impairment: Preliminary Findings from the Stroke Registry Investigating Cognitive Decline (STRIDE) study

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Introduction

The aging population in Hong Kong (HK) is rising at an unprecedented speed, with the elderly population (aged >65) more than doubling from 6.6% in 1981) to 13.3% in 2011 (Census and Statistics Department of Hong Kong Special Administrative Region, 2012a). By 2036, it is projected that 29% of the HK population will belong to this age group(Census and Statistics Department of Hong Kong Special Administrative Region, 2012b). With an impending aging crisis looming, the burden of age-dependent diseases such as cognitive impairment on the healthcare system are becoming urgent matters in need ofredress. In HK, the number of deaths due to dementia among people aged 60 or above has more than doubled from 2001 to 2009, and the estimated disability adjusted life years (DALYs) lost in this age group was up to 286,313(Yu, Chau, McGhee, Cheung, et al., 2012).

Cognitive impairment arising from vascular diseases is an important cause of dementia, while Alzheimer's disease is another cause. Vascular cognitive impairment (VCI) is considered a spectrum, which ranges from mild vascular cognitive impairment (MVCI) to vascular dementia (VaD). Both MVCI and VaD are defined by the presence of a cognitive disorder which is identified using neuropsychological testing together with either a history of clinical stroke or the presence of vascular disease identified by neuroimaging, although both vary in the number of cognitive domains compromised(Gorelick et al., 2011). Since stroke is the fourth leading cause of mortality in Hong Kong, there is a highprevalence of VaDof 4.3% accounting for 22.4% of all dementia(Lam et al., 2008).

Since the formulation of the 'disuse' hypothesis in 1991, which states that cognitive decline is directly associated withan underutilization of cognitive abilities, longitudinal studies havefocused on the impact of lifestyle factors in delaying dementia onset(Salthouse, 1991). There is a plethora of studies investigating the effects of physical activity and non-physical leisure activities, with such studiesconsistently showing that subjects who participate in these activities have better outcomes(Fratiglioni, Paillard-Borg, & Winblad, 2004). Engaging in these activitiesis able to reduce the risk of different types of dementia in the elderly population(Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Verghese et al., 2003; Wang, Karp, Winblad, & Fratiglioni, 2002). The ability of the brain to withstand age-related changes and disease pathology without the onset of symptoms is known as brain reserve, and meta-analyses have demonstrated that a high brain reserve resulting from mental and physical activities lowers dementia risk(Valenzuela & Sachdev, 2006).

Nevertheless, despite prodigious research interest in the role of modifiable lifestyle factors in dementia, data specific for VCI has been scarce. The effect of both physical and non-physical leisure activities on post-stroke cognitive function is currently unknown. Our study is the first to assess the effect of leisure activities both before and after stroke on the rate of cognitive decline. We hypothesized that these leisure activities would function to slow down cognitive decline after stroke, thus reducing the risk of developing post-stroke dementia.

Methods

Study Population

This paper presents preliminary findings from the ongoing Stroke Registry Investigating Cognitive Decline (STRIDE) study, which is a 5-year prospective cohort study that aims to investigate the mechanisms of early and delayed cognitive decline after a stroke or transient ischemic attack (TIA) event. The current cohort consists of 1298 Chinese patients with TIA, ischemic stroke, or hemorrhagic stroke that were enrolled from 2009 to 2010. Patients unable to communicate effectively for accurate cognitive assessment were excluded. Reasons included language barrier, presence of terminal illness, aphasiaand major psychiatric or medical comorbidity. Severe language impairment was defined by a score of <3 in the language component of the National Institute of Health Stroke Scale (NIHSS).TIA was defined as transient neurological deficits for < 24 hours with the absence of infarcts on neuroimaging. All cases with infarcts were classified as ischemic stroke, regardless of timing. Figure 1 depicts a flowchart of the recruitment procedure.

Data Collection

Participants were given a questionnaire at baseline (i.e. 3-6 months post-stroke) and at 15-18 month follow-up pertaining to lifestyle habits including their propensity to engage in physical and non-physical leisure activities. The types of activities were classified into a four-category system specific to the elderly lifestyle, which includesphysical, social, recreational and intellectual activities(Leung, Leung, & Lam, 2011). Patients were asked if they had participated regularly in an activity for the past year, and only subjects whose participation rate reached a minimum of three days per week were considered to be an active participant of the activity. Physical activity was further stratified into strenuous exercise, stretching exercise and mind-body exercise.

Psychologists assessed patients' cognitive function3 to 6 months after the index event under blinded conditions. Cognitive assessments such as Clinical Dementia Rating (CDR) scale(Morris, 1993), Cantonese Mini-Mental State Examination (MMSE)(Chiu, Lee, Chung, & Kwong, 1994)and Hong Kong's version of the Montreal Cognitive Assessment (MoCA)(Wong et al., 2009) were used.Possible confounding psychiatric factors such as depressive symptoms were measured using the Chinese Geriatric Depression scale (GDS) (Woo et al., 1994). The CDR score only accounted for symptoms attributed to cognitive decline and not to motor or mood deficiencies. Patients with a score ≥ 1 with suspected dementia at screening were invited for a more comprehensive clinical assessment to confirm diagnosis using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)(APA, 2000).

Demographic background and risk factors were collected(Knopman & Roberts, 2010). Hypertension was defined as those with a history of hypertension, on anti-hypertensive medications or clinically diagnosed with a blood pressure reading of >140/90 mmHg, averaged from three readings, 3 to 6 months after the index event. Diabetes mellitus (DM) was defined by a fasting serum glucose of ≥7.0mmol/L, postprandial serum glucose ≥11.1mmol/L or the use of oral hypoglycemic agents or insulin. Hyperlipidemia was defined as a total cholesterol level of ≥5.2mmol/L, low-density lipoprotein cholesterol level of ≥2.6mmol/L, triglyceride level of ≥1.70mmol/L or the use of lipid lowering drugs.Ischemic heart disease was defined as having a history of myocardial infarction or angina pectoris. Atrial fibrillation was diagnosed on the basis of at least one electrocardiogram before or during hospitalization. Smoking/alcohol intake was dichotomized as having ever or never smoked and having ever or never drank alcohol. Clinical history of congestive heart failure and prior TIA, ischemic and hemorrhagic strokes was also recorded.

At 15-18 month follow-up, 298 people were lost to follow-up or failed to provide data. Reasons included premature death, refusal to continue, physical weakness, departure from country and failure to communicate. Patients may also have switched groups from engaging in leisure activities to none, or vice-versa. Hence, the patients at baseline and at 15-monthswere different (Table 1 and Table 2). 222 patients switched from engaging in any activity to no activity while 141 patients switched from no activity to engaging in any activity.

Statistical Methods

All statistical analyses were conducted using SPSS Statistics, version 19.0. Patient characteristics at baseline and at 15 month follow-up were determined by descriptive summary statistics. Univariate linear regression was used for the selection of covariates, which included age, gender, education, GDS, hyperlipidemia and diabetes mellitus.Cerebral factors such as white matter hyperintensities (WMI), the number of big and small infarcts and lacunar infarcts were also covariates. Covariates found to be significant were included in a subsequent multivariate linear regression analysis.Hypertension and smoking were not predictors and thus excluded. All tests were 2-sided with a type I error rate of 0.05.

Results

Patient profiles at baseline were similar except for gender, education, and hypertension (Table 1). Patients in the activity group were more likely to be female, have hypertension and have higher education levels.Multivariate regression analyses revealed physical, recreational and intellectual activitiesto be positively associated with cognitive function at baseline ($p < 0.005$ for MOCA and MMSE; $p < 0.05$ for CDR), measured by regression coefficients as shown in Table 3

For the population at 15 month follow-up, their profiles were similar except for a history of prior TIA and stroke (Table 2). Patients who participated in physical activities ($p<0.005$ for MMSE and CDR, $p<0.05$ for MoCA), recreational activities ($p <0.005$ for MoCA, $p< 0.05$ for MMSE and CDR) or intellectual activities ($p <0.005$ for MMSE, MoCA, and CDR) fared better in all three neuropsychological tests than those who were inactive. Contrary to the population at baseline, the population at 15 month was able to benefit from social activities ($p<0.05$ for MMSE and MoCA).

Physical activities were further stratified into strenuous exercise, stretching exercise or mind-body exercise (Fig. 2). The difference in cognitive test scores was expressed in β.For the population at baseline, patients who participated in any of the three physical activities had better cognitive function than those who did not (Fig. 2A). However, patients from each physical activity category demonstrated better cognition based on different tests. Those who engaged in strenuous exercise had higher MoCA scores ($p<0.05$), while those who stretched had higher MMSE scores ($p<0.05$). Mind-body exercise participants had higher scores for both MMSE and MoCA ($p<0.05$).

The effects of physical activityon the cognitive function of the population at 15 month deviated from those at baseline (Fig. 2B). Like the baseline population, those who practiced mind-body exercises had higher scores in both MMSE and MoCA ($p<0.05$), but patients who stretched not only had higher scores in MMSE ($p<0.05$) but also better outcomes in terms of CDR ($p<0.005$). Those who engaged in strenuous exercise were unable to show improved cognition in any of the tests.

Discussion

At both baseline and 15-month follow up, there was a positive correlation between physical activity and cognitive function. This has been consistent with previous literature that examined the relationship between physical activity and cognitive improvement. However, the majority of studies have focused on physical activity as a lifestyle intervention factor post-stroke, while oursalso looked at pre-stroke physical activity as protection against post-stroke cognitive decline. It has been postulated that physical activity lowers the risk of cognitive impairment due to a reduction in systemic inflammation through the increased release of immunomodulatory factors(Foster, Rosenblatt, & Kuljis, 2011). Preclinical studies have demonstrated an increased release of brain-derived neurotrophin factors, which increased neuronal survival thus preserving brain elasticity in rats that performed aerobic exercise(Churchill et al., 2002; Neeper, Gomez-Pinilla, Choi, & Cotman, 1995). It enhances synaptic plasticity by altering synaptic structures and potentiating synaptic strength, especially in the hippocampus(Cotman, Berchtold, & Christie, 2007). Perhaps a more obvious explanation is the increase in cerebral blood flow which accompanies aerobic exercise, thus improving perfusion in the brain and preventing tissue deterioration(Fabre, Chamari, Mucci, Masse-Biron, & Prefaut, 2001). A study by Rand *et al* investigated the feasibility of a six-month exercise program in improving executive function, a cognitive domain frequently affected post-stroke(Rand, Eng, Liu-Ambrose, & Tawashy, 2010). The findings of the study suggest that frequent exercise twice a week for six months improved cognitive function in stroke patients. These findings were similarly replicated in another study with a six-month exercise program involving walking, showing improvements in executive function(Erickson & Kramer, 2009).

Although less extensively researched, our findings suggest that engaging in intellectual activities may also protect against post-stroke cognitive decline. Education was a predictor of cognition in our study, andthisconfirms previous epidemiological studies that the level of educational attainment reduces the risk of dementia andprotectsagainst post-stroke and post-TIA cognitive decline (Sachdev, Brodaty, Valenzuela, Lorentz, & Koschera, 2004; Valenzuela & Sachdev, 2006). The reason for this is unclear, but some have postulated that education and intellectual stimulation is a direct correlate of cognitive reserve, which provides a larger margin of decline before deficits become symptomatic. A meta-analysis by Pendlebury *et al* found that low education levels was a significant predictor of post-stroke dementia(Pendlebury & Rothwell, 2009).

Our results suggest a protective effect of recreational and social activities on post-stroke cognitive function. As compared with physical activity, there is a current lack of mechanistic studies investigating the role of recreational and social activities in improving cognitive function. This is perhaps owing to the fact that it is difficult to define recreational and social activities given the diversity of options. One study in a Chinese population has however, looked at the effect of mental and social activities on cognitive function(Wang et al., 2013). This is highly relevant given that the population enjoys activities that are frequency engaged in by the Chinese population, including mahjong and the opera, which may suggest generalizability to any countries that possess a large Chinese diaspora.An interesting finding of the study was that different types of activities were found to be protective against different aspects of cognitive function. For example, mental activity was associated with executive function, physical activity with memory and language and social activity with global cognition (Wang et al., 2013). Due to the complementary nature of the activities, Wang *et al* found a dose-response pattern such that engagement in a wider variety of activities, the stronger the association with improved cognitive function.

When physical activities were stratified into strenuous, stretching, and mind-body exercise, all of them were beneficial. Strenuous and stretching is most likely related to the aforementioned physiology on inflammation reduction and strengthening of synapsis, whereas mind-body exercise is similar to the build-up of cognitive reserve by intellectual stimulation.

Although the preliminary results from the STRIDE study provide valuable insight into the modulation effect of leisure activities on post-stroke cognitive decline in the Chinese population, further studies are needed to strengthen our current conclusions. It will be of interest to look at whether engaging in lifestyle activities both pre-stroke and post-stroke is more protective against post-stroke cognitive decline as opposed to isolating the analysis to only pre-stroke or only post-stroke lifestyle activities. Moreover, a longer follow-up period will aid in determining whether lifestyle activities have a long-term protective effect. Determining the specific type of activity under each of our categories that is most effective in protecting against cognitive decline, as well as the necessary duration, frequency and intensity, will further inform current practice. It is widely accepted though that long-term, frequent exercise is most beneficial(Ahlskog, Geda, Graff-Radford, & Petersen, 2011). Conducting a randomized, controlled trial of engaging in leisure activities may provide definitive validation of our current findings.

Decline in cognitive function after stroke is well-documented in the literature, with greater than 30% of patients experiencing post-stroke cognitive decline between three to 15 months after stroke, with severity ranging from mild cognitive impairment to dementia(Ballard, Rowan, Stephens, Kalaria, & Kenny, 2003). The prevalence of stroke in the elderly population of Hong Kong (aged 65 and above) has been on the rise since 1998, reaching 4.9% in 2008(Yu, Chau, McGhee, Chau, et al., 2012). Given the prevalence of stroke among the elderly population compounded by the aging population in Hong Kong, the burden of post-stroke cognitive decline on the healthcare system has wide-reaching implications. The prevalence of post-stroke cognitive impairment is high at 32% three years after stroke(Patel, Coshall, Rudd, & Wolfe, 2003). The STRIDE study is the first study to investigate the effect of lifestyle activities on post-stroke cognitive decline within a Chinese population. It is apparent from the above discussion that our preliminary findings are in accord with other published studies; however, it is necessary to bear in mind the difficulty in making direct comparisons due to the use of different neuropsychological batteries, which each assess different domains of neuropsychological function. While our analysis is limited to preliminary data, the results thus far provide much needed validation in a Chinese population of the importance of engaging in various activities as a protective mechanism against post-stroke cognitive decline.

In addition, emphasizing the benefits ofphysical activity has only been moderately useful in reducing physical inactivity(Wen & Wu, 2012). Mimicking strategies used in tobacco control, which elicit negative emotions through the use of slogans and graphic photos detailing the undesirable health effects associated with smoking, may provide people with greater impetus to engage in physical activity(Durkin, Brennan, & Wakefield, 2012). These scare tactics scored higher on memorability, as well as being more effective at increasing knowledge, changing smoking attitudes and increasing quitting intentions(Durkin et al., 2012). They were also responsible for cutting smoking rates in Australia to an all-time low(Chapman, 1999). Adopting scare tactics, in addition to promoting the positive effects of physical activity, will serve to more effectively and efficiently change people's attitudes towards physical activity, resulting in greater value being placed on health.

There are demonstrated deficiencies in stroke knowledge in HK, with one-third of the public incorrectly definingstroke(Cheung, 2001) and 91% beingunable to identify all stroke-warning signs(Lau, 2012). This can result in the delayed seeking of medical attention – a situation that can be negated with better health promotion (Maasland et al., 2011). To remedy this knowledge deficit, targeted and continuous health education is imperative in creating a healthier society. Health education programs that specifically aim to addressan individual's needs and concerns by providing tailored advicecombinedwith repetition has appeared to be more successful than general advice(Maasland et al., 2011). Effective implementation of this strategy requires collaboration with Non-governmental Organizations ('NGOs'), such as the Hong Kong Stroke Fund, which already has established public education programs(Lau, 2012). In addition, they can broadcast specialized programs concerning stroke on the radio, which has been shown to bepopular in the elderly population(Chan & Cheung, 2009).

In addition to promoting an active lifestyle, the Government must ensure and provide affordable solutions to achieving an active lifestyle. To facilitate this, governments must enhance access to leisure activities by providingthe necessary funds and subsidies to implement programmes that aim to target all age groups, with greater priority to the elderly who have the highest risk of stroke("Acute Stroke," 2010). Our study findings suggest that a programmepromoting and teaching mind-body exercises (such as tai-chi) will be highly beneficial and this is consistent with other studies that such exercises help in preserving global cognitive ability in healthy elders(Lam et al., 2012).According to the HK Government, "30 minutes of moderate exercise every day is beneficial to health" (Rand et al., 2010). These guidelines provide advice on the intensity, frequency and duration of physical activity that is necessary to produce visible health benefits. However, with the existing guidelines,the general public may be under the misconception that any physical activity short of the guidelines will not be beneficial, resulting in an all or nothing attitude. As such, new, revised guidelinesshould be established so that people understand that while the guidelines provide for the optimum amount of physical activity, that anything less will still be beneficial. Current doctors should take a more proactive role in relaying this message through the prescription of light but regular exercise.

The Role of Medical Students

Medical students play an intermediary role between government authorities and the general population and aid in the execution of governmental health interventions. Their accessibility to the community allows for the identification of local problems from a grass-roots level as well as the effective implementation of government policies.

Given their medical knowledge, integration of medical students into the community provides a platform for them to inform locals of the importance of leisure activities in protecting against post-stroke dementia. In collaboration with district authorities and NGOs, medical students can initiate health campaigns in the form of exhibitions, workshops and fundraising events to promote awareness of VCI and stroke. For example, a fundraising event organized by the National Stroke Association in the United States raised over USD $30,000 in the past three years, with the aim of increasing stroke awareness amongst small-town communities(Bruttell, 2013). Events such as these can provide much needed funding for stroke NGOs to initiate local projects in the future. Moreover, the unique nature of Hong Kong's high population density provides power for mass promotion, especially when the community unitesthrough demonstrations to increase awareness of the importance of physical activities in protecting against VCI and stroke.

Medical students can also encourage physical activity in younger generations, providing a strong foundation for the development of long-term healthy behavior that continues into adulthood. This eases the burden on the healthcare system through a reduction in the prevalence of VCI and stroke.

In aid of mass media campaigns by the government, medical students can create websites and viral YouTube videos to promote health awareness of VCI and stroke. The award-winning "Aphasia Recovery Connection" website in the United States is an online support group for aphasia victims and their families to share their experiences with the community(Aphasia Recovery Connection). Media platforms can incorporate health information with the personal experiences of those affected by stroke, bringing the message home. Not only does thispromote awareness of VCI and stroke in a more personal and inspiring way, it also creates a support network for stroke survivors, allowing them to find strength in each other.

More importantly, instead of relying on the community to attend public health programs, medical students can aid in bringing the information to the community byeducating social workers who can relay the message during household visits. Home-visit programs are feasible at low costs due to Hong Kong's densely populated households and close proximity. Through routine visits, the aim is to engageless-activeindividuals in various activities such as informal chats and doing mind-body exercises like *tai-chi*, thus increasing their social, recreational, and intellectual stimulation while cultivating their interest in these activities. The goal is that they will continue to engage in these activities in the long-term, thus aiding in the reduction of post-stroke deterioration.

Limitations

There are several limitations in this study. First, since we excluded patients who were afflicted by severe aphasia, a common manifestation of severe stroke, there could have been selection bias in favor of younger and healthier elderlies that is unrepresentative of the general population. This might explain the lower frequency of incident dementia observed in this study when compared with other studies (data not shown)(Pendlebury, 2012).Second, the fact that this is a hospital-based study may have underestimated the number of patients with very mild stroke. Radiologically, about half of the cases had CT scan only, which is not ideal to visualize small infarcts, infarcts located in the posterior fossa and mild severity WMI. Even though linear regression adjusted for these cerebral factors, it is possible that some of these pathologies failed to be diagnosed and confounded the results.Third, the neuropsychological test scores can be affected by an individual's level of education, as those with a higher level of educational attainment may find the questions easier than those with a lower educational level. Lastly, there wasalso significant heterogeneity in the baseline characteristics of the two groups as we were unable to apply a matched-pairs design. However, we have adjusted for potential confounders in the regression analysis.

Conclusions

Preliminary findings from the STRIDE study highlighted the beneficial effects of leisure activities before and after stroke in slowing cognitive decline.Leisure activities such as physical, social, recreational and intellectual activity were all independent predictors of higher cognitive scores. With respect to physical activity, patients who partook in stretching and mind-body exercises achieved superiority in cognitive tests in both the baseline and 15 month follow-up populations. Longer-term follow-up is warranted to completely assess the long-term prognosis of cognition and to elucidate the hazard ratio of VCI between those who do and do not actively engage in leisure activities.

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Figures and Tables

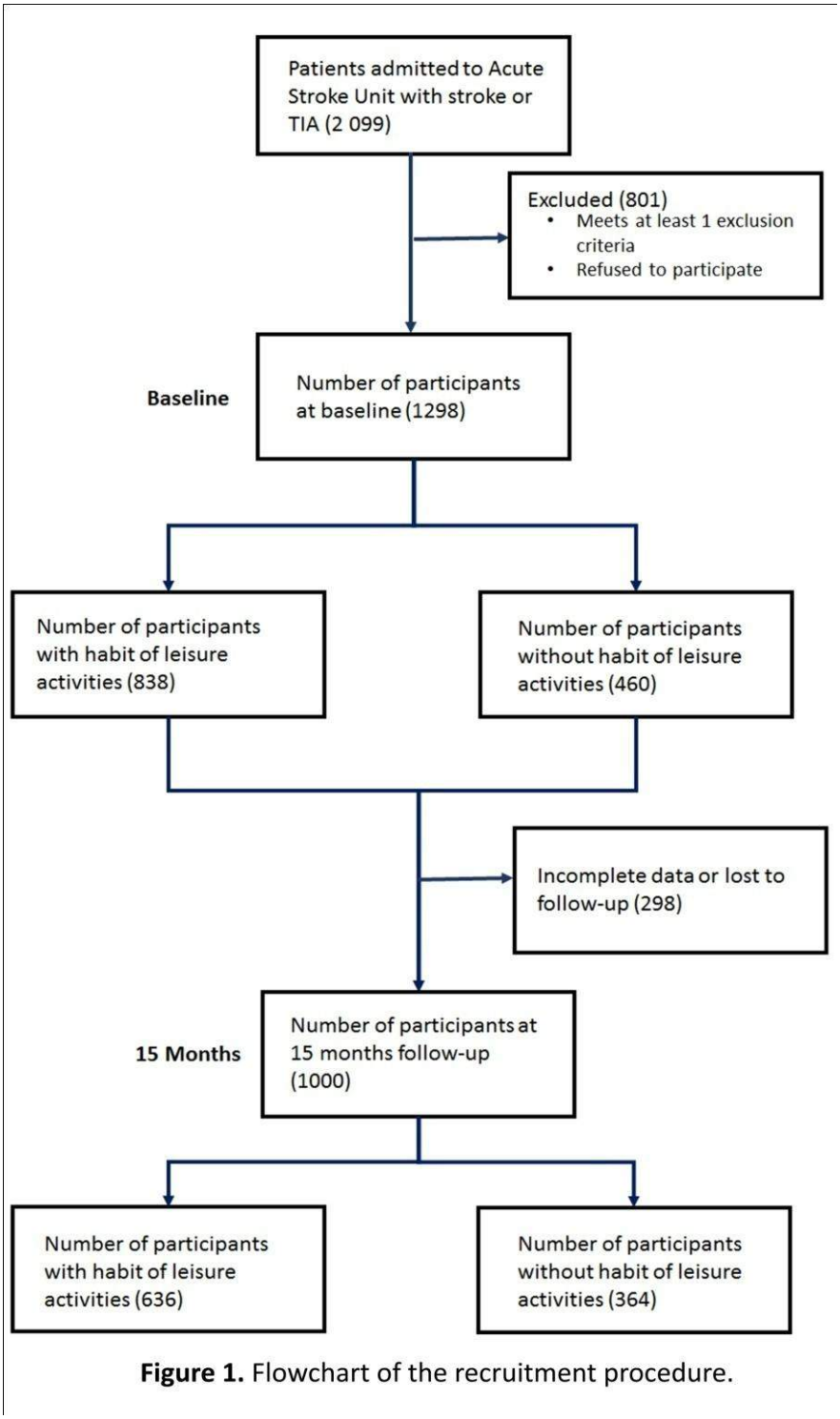

Figure 1. Flowchart of the recruitment procedure.

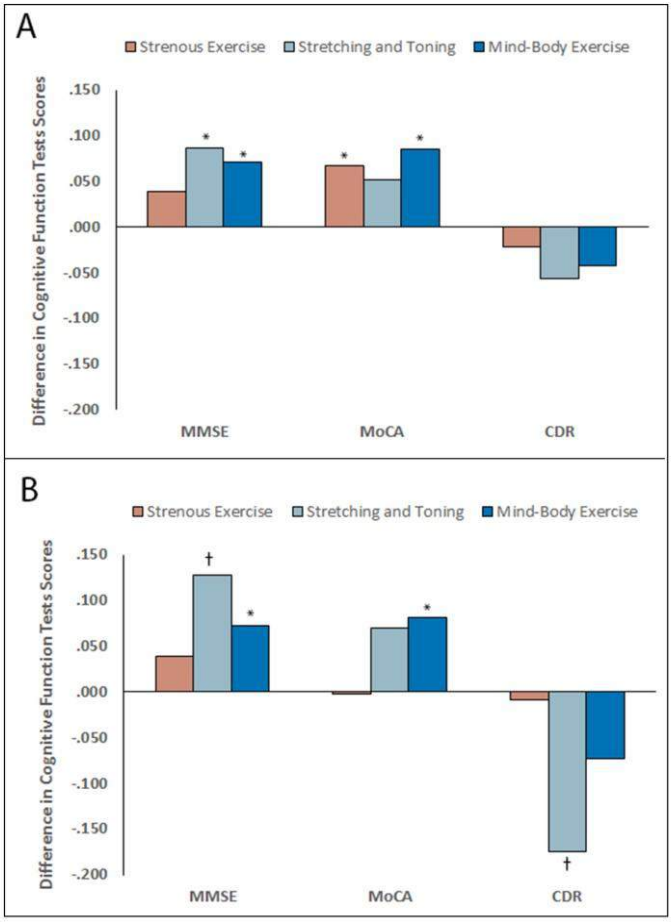

Figure 2. Association of each type of physical activity with cognitive function using multivariate linear regression. Changes in cognitive function are expressed as β coefficient. Panel A indicates the effect of each physical activity for the baseline population, while panel B indicates the effect of each exercise for the 15 months follow-up population. All scores have been adjusted for age, gender, education, Geriatric depression symptoms, DM, hyperlipidemia, white matter hyperintensities, big and small acute infarcts and lacunar infarcts. *P < 0.05; †P < 0.005

Table 1. Patient Characteristics with and without Leisure Activities at Baseline*.

Variable	Any Activity (N = 838)	No Activity (N =460)	P-value	Total (N = 1298)
Age (y)	71.10±11.09	68.34±12.70	0.215	70.28±11.60
Male sex – no. (%)	485 (53.5)	221 (57.3)	<0.001	709 (54.6)
Education (Years)	5.50±4.84	4.87±4.68	0.030	5.31±4.80
Body-mass index	23.89±6.04	24.23±3.76	0.309	23.97 ± 5.5
Hyperlipidemia – no. / total no. (%)	521 (57.1)	225 (58.3)	0.369	746 (57.5)
Hypertension – no. / total no. (%)	625 (68.5)	233 (60.4)	0.019	858 (66.1)
Diabetes Mellitus – no. / total no. (%)	329 (36.1)	126 (32.6)	0.367	455 (35.1)
Prior stroke or TIA – no. /total no. (%)	194 (21.3)	80 (20.7)	0.826	274 (21.1)
Current smokers – no. / total. (%)	108 (11.8)	51 (13.2)	0.068	159 (12.2)

*Plus-minus values are means ± SD.

Table 2. Patient Characteristics with and without Leisure Activities at 15 months follow-up*.

Variable	Any Activity (N = 636)	No Activity (N =346)	P-value	Total (N = 1000)
Age (y)	69.46+10.37	70.82+12.870	0.085	69.98±11.64
Male sex – no. (%)	354 (55.6)	192 (52.0)	0.278	584 (58.4)
Education (Years)	5.69+4.850	5.26+4.571	0.171	5.57±4.750
Body-mass index	23.95+3.57	24.16+8.93	0.713	24.06±5.73
Hyperlipidemia – no. / total no. (%)	380 (59.7)	210 (56.9)	0.766	630 (63.0)
Hypertension – no. / total no. (%)	417 (65.5)	243 (65.9)	0.766	704 (70.4)
Diabetes Mellitus – no. / total no. (%)	222 (34.9)	127 (34.4)	0.956	366 (36.6
Prior stroke or TIA – no. /total no. (%)	120 (18.87)	95 (26.09)	0.012	215 (21.4)
Current smokers – no. / total. (%)	70 (11.01)	51 (14.01)	0.1	121 (12.2)

*Plus-minus values are means ± SD.

Table 3. Associations of Cognitive Function per Standard Deviation of Various Types of Pre-stroke Activity at Baseline and Post-stroke Activity at 15 months.

Characteristics	B-coefficient (95% CI)		β-coefficient (95% CI)	
	Baseline	15 Months	Baseline	15 Months
MMSE				
Physical activities	1.71 (0.90, 2.52)†	1.68 (0.79, 2.57)†	0.13†	0.14†
Social activities	1.20 (-0.37, 2.76)	1.72 (0.25, 3.19)*	0.05	0.09*
Recreational activities	1.20 (0.44, 1.97)†	1.21 (0.29, 2.12)*	0.10†	0.10*
Intellectual activities	1.95 (1.21, 2.69)†	3.69 (2.76, 4.63)†	0.17†	0.30†
MoCA				
Physical activities	1.42 (0.52, 2.32)†	1.02 (0.03, 2.01)*	0.10†	0.07*
Social activities	0.56 (-1.14, 2.26)	2.11 (0.48, 3.74)*	0.02	0.09*
Recreational activities	1.39 (0.57, 2.21)†	1.64 (0.65, 2.62)†	0.11†	0.12†
Intellectual activities	1.72 (0.91, 2.53)†	3.74 (2.70, 4.77)†	0.13†	0.27†
CDR				
Physical activities	-0.61 (-1.10, -0.12)*	-1.20 (-1.84, -0.55)†	-0.09*	-0.16†
Social activities	-0.63 (-1.65, 0.39)	-0.34 (-1.41, 0.72)	-0.05	-0.03
Recreational activities	-0.53 (-1.03, -0.030)*	-0.72 (-1.38, -0.06)*	-0.08*	-0.10*
Intellectual activities	-0.50 (-1.00, -0.003)*	-2.18 (-2.87, -1.50)†	-0.08*	-0.30†

MMSE, Cantonese Mini mental state examination; MoCA, Hong Kong's version of Montreal cognitive assessment; CDR, clinical dementia rating. All scores have been adjusted for age, gender, education, Geriatric depression symptoms, diabetes mellitus, hyperlipidemia, white matter hyperintensities, big and small acute infarcts, and lacunar infarcts.

*$P < 0.05$; †$P < 0.005$

SCIENTIFIC PAPER COMPETITION – INDIA

TITLE:ASSESSMENT OF HELPLESSNESS AND ITS CORRELATES WITH SOCIO DEMOGRAPHIC FACTORS&DISEASE SEVERITY IN COPD PATIENTS IN TERTIARY CARE HOSPITALS OF DELHI

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ABSTRACT

BACKGROUND: Chronic Obstructive Pulmonary Disease(COPD) mortality in India is estimated to be amongst the hi ghest in the world. India has approximately 30 million (1 in 50 people) COPD cases which are expected to increase by 34 per cent by 2020. Although the identification and management of physical signs and symptoms of Chronic L ung Diseases has improved but the psychosocial burden is often unrecognized and neglected. Presence of psychol ogical distress creates greater dependence on others, less effective self management of respiratory symptoms, and l onger hospital stays. Therefore we have undertaken this study to assess degree of helplessness among COPD patie nts and socio-demographic factors influencing it.

MATERIALS AND METHOD:A cross sectional study was carried out in 3 tertiary care hospitals of Delhi with 224 par ticipants aged 40 years or above. A pre-designed, pre-tested COPD Helplessness Index (CHI) questionnaire was ad ministered to subjects after an informed consent. GOLD(Global Initiative for Chronic Obstructive Lung Disease) stagi ng system for COPD was used to categorize patients based on their disease severity. The analysis was done on **S**tat istical **P**ackage for **S**ocial **S**ciences (SPSS) version 17.0. 'p-value' less than 0.05 was considered significant.

RESULTS: The data of 224 patients diagnosed with COPD was analysed. CHI related directly with COPD severity ($p < 0.001$). Elderly patients, males, illiterates & smokers were found to have a higher CHI score showing helplessness in study subjects.

CONCLUSION: There is a strong correlation between helplessness and pulmonary function with Age, gender, literac y and smoking status having a significant influence on the psychological state of COPD patients. An integrated effo rt on the part of the patients, doctors and the society is required to reduce the burden of COPD. Peer support and counselling can play a major role in alleviation of the associated psychological problems. Medical students can cont ribute towards spreading awareness by providing relevant health education.

FULL PAPER

TITLE: ASSESSMENT OF HELPLESSNESS AND ITS CORRELATES WITH SOCIO DEMOGRAPHIC FACTORS & DISEASE SEVERITY IN COPD PATIENTS IN TERTIARY CARE HOSPITALS OF DELHI, INDIA

INTRODUCTION:

According to WHO Chronic Obstructive Pulmonary Disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible.

COPD is a major cause of morbidity and mortality across the globe.[1]It affects an estimated 210 million people worldwide.[1]It is estimated that by 2030 COPD will become the third leading cause of death worldwide.[1]

Low- and middle-income countries like India shoulder much of the burden with 90% of the total COPD related deaths, where effective strategies for prevention and control are not always implemented or accessible. As mentioned in the WHO Global InfoBase (2011),India contributes a significant and growing percentage of COPD mortality estimated to be amongst the highest in the world.[2]India has approximately 30 million (1 in 50 people) COPD cases which are expected to increase by 34 per cent by 2020.

Despite this enormous health burden, COPD remains an unknown, under-researched and disease in India and there is lack of awareness among patients regarding prevention and care.

COPD involves a gradual and progressive decline in lung function which results in increased dyspnoea and reduced ability to perform daily activities. The experience of breathlessness can be distressing and difficult to understand and control[3]. As a result COPD significantly affects mental health because of its impact on daily activities, sleep and social life of patients[3]. It is reported that psychiatric disorders are more prevalent in obstructive lung patients than general population[4-7] Although identification and management of the physical signs and symptoms of Chronic Lung Diseases (CLDs) has improved but the psychosocial burden is often unrecognised and neglected.[3]A study (Arne et al ,2007) suggests that the psychological morbidity could be equal to or even greater than the effect of early physical symptoms themselves. Psychological factors can create a vicious circle, with escalating breathlessness, physiological arousal and panic. It has been shown that there is a strong relation between psychological factors, reported levels of dyspnoea and age level in the advanced stages of COPD. The presence of psychological distress creates greater dependence on others, less effective self-management of respiratory symptoms, and longer hospitalstays. Psychological factors may also be a risk factor for exacerbation of these pulmonary disorders.[4]

COPD Helplessness Index (CHI)is a new tool for measuring feelings of helplessness among patients with COPD, and is associated concurrently with psychological health status as developed and validated by Omachi, et al[8].

Patient self-management is believed to be a key element of successful COPD treatment.[9]However, self-management practices in COPD can be complex and burdensome. Psychological factors play a role in how well patients respond to attempts to improve their self-management skills in COPD.

If patients are to live with chronic disease and maintain a good quality of life, it is imperative that these issues are not only recognised but also managed.

We therefore sought to assess, in a specific Indian context, helplessness in COPD patients and its co-relation with disease severity and socio-demographic factors and design suitable management strategies. This will enable us to help patients cope better in their life long struggle with this debilitating disease.

MATERIALS AND METHODS:

Study Setting:

A Cross Sectional observational study was carried out over a period of 2 Months (20th September 2013 to 20th November 2013) in Chest OPD, Department of Internal Medicine in Lok Nayak Hospital under Maulana Azad Medical College, L.H.M.C and S.K Hospital and Hindu Rao Hospital in Delhi in a sample size of 224 diagnosed COPD patients.

Study Subjects:

All patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) attending the chest OPD under the above mentioned study period and giving informed consent were included in the study.

Inclusion Criteria

Adult cases of COPD with or without complications aged 40or above.

Exclusion Criteria

1. Very severe cases unable to give informed consent and talk.
2. Patients with cardiac co-morbidities,renal failure, hepatic failure and with known psychiatric illness and all types of diabetes.

Data Collection

Data was collected using pre – tested interview schedule after getting informed consent.

A pre-designed, pre-tested CHI questionnaire was administered to subjects after an informed consent.

The schedule included items on socio-demographic factors(Name, Age, Sex, Occupation, Religion, Literacy, Tobacco status), complaints, problems, observation, Intake of medication, clinical examination and laboratory examination.

Study Tools

Baseline Questionnaire To determine socio-demographic factors i.e. Name, Age, Sex, Occupation, Religion, Literacy & Tobacco status.

COPD Helplessness Index (CHI) Questionnaire: - The CHI is an internally consistent and valid measure, concurrently associated with health status and predictively associated with COPD exacerbation. The CHI questionnaire consists of 15 questions related to self-management of COPD. Each item was rated using a 0 to 4 point Likert format by selecting one of the following response categories: "strongly agree,","agree," "neutral / neither agree nor disagree," "disagree," or "strongly disagree."In its final form, the CHI has a score range of 0 to 60, with higher scores reflecting greater helplessness.

Pulmonary Function Test: -Group of tests that measure how well the lungs take in and release air and how well they move gases such as oxygen from the atmosphere into the body's circulation. FEV_1 (%predicted) i.e. maximal amount of air one can forcefully exhale in one second was noted to determine the severity of COPD.

Data Entry and Analysis

GOLD(Global Initiative for Chronic Obstructive Lung Disease) Staging System for COPD: - A validated system that classifies people with COPD based on their degree of airflow limitation (obstruction). GOLD COPD staging uses four categories of severity for COPD, based on the value of FEV_1 –

Stage I	Mild COPD	$FEV_1 \geq 80\%$ normal
Stage II	Moderate COPD	FEV_1 50-79% normal
Stage III	Severe COPD	FEV_1 30-49% normal
Stage IV	Very Severe COPD	FEV_1 <30% normal, or <50% normal with chronic respiratory failure present*

It was used to categorize the patients into stages based their disease severity.

The data was entered in **S**tatistical **P**ackage for **S**ocial **S**ciences (SPSS) version 17.0 and summarized through frequency distributions and suitable graphs were ma de to enhance visual appeal.Quantitative variables were summarized in terms of mean±s.d and their correlations with qualitative variables was established using either ANO VA or Unpaired t-test.

A p-value < 0.05 was considered to be statistically significant.

RESULTS:

A.GENERAL CHARACTERISTICS OF THE STUDY POLULATION

TABLE 1: AGE AND GENDER WISE DISTRIBUTION OF THE STUDY SUBJECTS

There were 176 males (78.6%) and 48 females (21.4%). Maximum number of COPD patients (=72, 32.1%) were in the age group of 60-69 years followed by those in >= 70 age group (=54, 24.1%).

FIGURE1: AGE AND GENDER WISE DISTRIBUTION OF THE STUDY SUBJECTS

FIGURE 2: DISTRIBUTION OF STUDY SUBJECTS BY RELIGION

FIGURE 3: LITERACY LEVEL OF STUDY POPULATION

Among the study subjects 68.8% were illiterate.

FIGURE 4: SMOKING STATUS AMONG THE STUDY SUBJECTS.

75.9% of subjects were present or past smokers with maximum being former smokers (=96, 42.9%).

TABLE 2 : CATEGORISATION OF PATIENTS ACCORDING TO GOLD STAGES OF COPD SEVERITY

Maximum number of patients (41.1%) belonged to GOLD Stage 3 (FEV1% predicted= 30-49%) followed by Stage 4 (FEV1% predicted< 30%) with 28.6% patients.

FIGURE 5: CATEGORISATION OF PATIENTS ACCORDING TO GOLD STAGES OF COPD SEVERITY

FIGURE 6:DISTRIBUTION OF COPD HELPLESSNESS INDEX(CHI)

The mean of CHI score for the study subjects is 26.59 ± 7.62.

B.CO-RELATION OF CHI WITH SOCIO-DEMOGRAPHIC FACTORS AND COPD SEVERITY

TABLE 3: CO-RELATION OF CHI AND COPD SEVERITY

Increasing severity of COPD was linked to a higher CHI score showing helplessness. p value < 0.001.

TABLE 4: CO-RELATIONS BETWEEN AGE, FEV1 (%PREDICTED) & CHI SCORE

Age has a significant correlation with FEV1% predicted (p value <0.001) as well as CHI score (p value=0.019) i.e. if age is increasing the value of FEV1% predicted will also d ecrease. Similarly with increase in age, the value of CHI will also increase. Also, FEV1% is significantly correlated with CHI Score (p < 0.001) .

FIGURE 7: CO-RELATION BETWEEN AGE & CHI SCORE

FIGURE 8: CO-RELATION BETWEEN FEV1(%PREDICTED) & CHI SORE

TABLE 5: CORRELATION OF CHI AND SEX

The CHI score was significantly higher among males (27.48± 7.47) than females (23.33±7.35). p value =0.001

TABLE 6:CO-RELATION BETWEEN CHI SCORE AND RELIGION

The CHI score was significantly higher among Hindus (27.47) as compared to Muslims (25.33).(p = 0.038)

TABLE 7: CO-RELATION OF CHI SCORE AND LITERACY

The mean CHI score was significantly higher in illiterates (27.86) than in literates (23.80).(p <0.001)

TABLE 8:CO-RELATION OF CHI AND SMOKING STATUS

CHI Score was found to be highest amongst current smokers as compared to other categories.

The difference in CHI score between the groups based on smoking status was found to be statistically significant. (p <0.001)

DISCUSSION:

The present study examines correlation of helplessness in COPD patients with COPD severity and socio-demographic factors. The tool used to assess the same was the COPD Helplessness Index (CHI) Score.

The mean CHI showed a consistent & statistically significant ($p < 0.05$) increase with rising severity (measured as per the GOLD guidelines).This can be attributed to increasing inability to work leading to low self-esteem, sense of worthlessness, financial burdens of the disease, poor mobility, social isolation and loss of independence with rising severity. The inability to carry out daily living activities makes the patient very dependent on others. This is consistent with a study by Manen et al in 2002according to which risk of depression in COPD patients found to be 2.5 times greater for severe COPD when compared to patients in the control group.[10]

The mean CHI was found to be significantly higher amongst illiterate patients as compared to the literates. This can be attributed to the lack of awareness about the disease, treatment modalities,

inability to comprehend posters, brochures and inadequacy to follow the guidelines, lifestyle changes recommended by the doctor such as proper techniques to use inhaler. Patients with reduced health literacy may inherently have more difficulty comprehending medical information. Such individuals are thus more likely to be non-compliant due to misunderstandings (Rand, 2005).Such Patients are likely to under-use maintenance therapy and symptom relieving drugs are often over used (Hand and Bradley, 1996).[11-12]Studies in asthma and COPD have shown that adherence can be less than 50% of prescribed medication(Rand,2005).[11]

Analysis showed a relationship of CHI with age, higher age showing a higher CHI score.

Problems of elderly include dependence on family members for hospital visits, lack of support due growing nature of nuclear families in urban India. Additionally due to cognitive impairment in elderly COPD patients, much of what is said in any medical consultation is forgotten soon after it ends (Ley 1979) (Allen and Ragab 2002).[13-14]

This result is in contrast to the findings of other studies[15-19] in which young patients present greater levels of anxiety and older patients report fewer emotional problems (depression, rage and frustration) as they present less suffering in coping with the disease.

Study revealed a significant correlation between mean CHI score and smoking status, the score being

higher in former & current smokers than in non smokers. As per a study (Payne et al., 1991;

Timmereck & Randolph, 1993; Thornton, Lee, & Fry, 1994; Parrot, 1995;Rowe, Fleming, Barry, Manwell, & Kropp, 1995) the risk of depression amongst smokers is twice as great as non-smokers in a sample population of COPD patients. Addiction and the inability to quit are some contributing factors for helplessness.[20-24]

LIMITATIONS:

1.Other Socio-demographic factors like occupation and economic status which can also infuence CHI were not assessed.

2.Since the study was done in non-randomly selected government hospitals, selection bias might be present. Hence the findings can not be a reflection of the general population.

3.Co-morbidities such as osteoporosis which can also contribute to helplessness were not considered.

CURRENT HEALTH POLICY-THE INDIAN SCENARIO:

Guidelines developed under the WHO-Government of India biennium programme (2002-03) are standardised for COPD management in India.They essentially incorporate general GOLD recommendations. Major alterations include a greater stress on clinical criteria, exclusion of diagnosis of tuberculosis, and a three-tier approach at different levels of healthcare, especially the primary and secondary care levels.[25]

Despite the revised guidelines and the fact that COPD is a leading cause of death and suffering in India, it does not have a National Prevention and Control Programme.[26] It still remains a neglected Cinderella disease. Considering the fragmented nature of the healthcare delivery industry in India, there are no big centers of excellence in India providing protocolized rehabilitation services as in the western world. Mostly individual physician initiatives lead to rehabilitation in informal un-structured manner.

RECOMMENDATIONS:

Addressing the psychological effects of COPD

As concluded in the study, COPD progression is intricately linked with the development of helplessness, frustration and hopelessness. Battling these requires an integrated effort on the part of the patients, doctors and the community.

Peer Support: Patient oriented collaboration groups or support groups like the Better Breather's Clubs (USA) should be established to provide patients with a setting to exchange information and experiences and participate in social activities. This improves self management.

Health Education: Health education is an integral component of aCOPD management program. This should include aspects of proper training on inhaler technique, importance of taking timely medications, avoiding risk factors like smoking and environmental air pollution.

Counselling: The physicians tend to overlook the psychological needs of the patient due to the time restriction and the overload of patients . The doctor-patient efficient communication is lacking .Counselling consisting oflife-style changes ,engagement in physical activity, seeking help from family should be stressed.

Quit Smoking

Prophylaxis begins with the step of quitting smoking. Anti-smoking campaigns using posters, SMS, campaigns, street plays should be started. Taxes on cigarette packs should be increased to reduce the average consumption. Nicotine replacement therapies in the form of nicotine gums such as the recently launched Indian tobacco company product "kwiknic" which is low priced. It is available in all the local shops and is easily accessible to the low income groups who comprise the majority of smokers.

Exercise and Fitness

Physical activities like walking or cycling along with breathing exercises increases respiratory muscle strength, clears sputum. Excercise and fitness should be promoted in the form of walking, yoga phyisiotherapy sessions.

Ancient Indian Yoga exercises like *pranayam (art of breathing control)* have been proved to improve breathing and have a pacifying effect.

According to the PLATINO study (Menezez,2005) dyspnoea, wheeze and exacerbations are independently related to BMI. Hence, weight management and fitness are crucial for improved health in COPD patients

Management of Acute Exacerbations

Advice the patient to seek medical help in managing acute exacerbations. Follow up of patients physical and mental conditions prevents exacerbations. Doctors should be well trained to respond promptly to symptoms of exacerbation.

Health Care System

Although bronchodilators are provided to the patients free of cost in the government hospitals and health care centres in India but these are generally out of st ock and unavailable. This makes it difficult for the patients coming from far off places to receive medicines leading to low patient adherence in COPD. Equitable distributio n of the resources by improving stock supply and increasing number of health care centres will improve patient compliance.

Development of centres of excellence in copd in each state of the country making healthcare services accessible.

Supplemental Oxygen

Patients often resist using oxygen therapy because of the social stigmas associated with it. Patients should be counselled on accepting supplemental oxygen.

Routine Check-ups

Follow up of lung indices as routine is the gold standard for management. Spirometry as well as multidimensional assessment tools like BODE and DOSE index c an be used to assess the course of the disease and design revised treatment plans.

Regular screening for co-morbidities like Cardiovascular problems and lung.

Spreading Awareness

Our government can declare a particular month as COPD month where awareness is taken to a national level. For example, November is COPD month in USA.

ROLE OF MEDICAL STUDENTS

As future doctors, medical students can play a pivotal role in the healthcare system.

They can organize and actively participate in educational campaigns conducted in poor communities where people do not know about COPD and its proper ma nagement .

Awareness can be increased through information booths in malls, health fairs, schools and other community events. Advertising can be done through posters which can be put up in their own hospitals and nearby health centres

Teaching people the importance of exercise and training intensity through seminars arranged in rural and remote areas can help reduce mortality in COPD patie nts

Regular screening can be carried out by the medical students under senior supervision to identify cases for early diagnosis and management

Students through their campaigning can encourage pulmonary rehabilitation.Students can provide assistance to medical personnel in these centres to improve t he quality of service provided. Students should be assigned 2-3 COPD cases for tailoring individual requirements such as nutrition ,psychological councelling.

Students can put forward proposals to government to increase resource mobilization in rural and remote areas.This will improve accessibility of medical facilities.

Taking up research projects to improve understanding and management of the disease

CONCLUSION:

There is a strong correlation between helplessness and pulmonary function with socio-demographic factors having a significant influence on the psychological st ate of COPD patients.An integrated effort on the part of the patients, doctors and the society is required to reduce the burden of COPD. Peer support and counselling can play a major role in alleviation of the associated psychological problems. Medical students can contribute towards spreading awareness by providing relevant health educati on.

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Figures and Tables

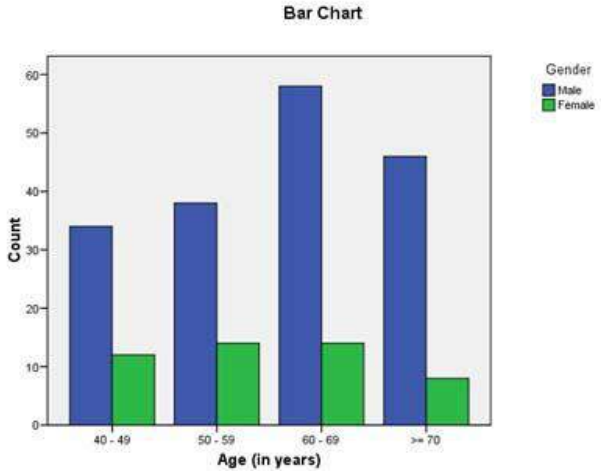


Figure1.

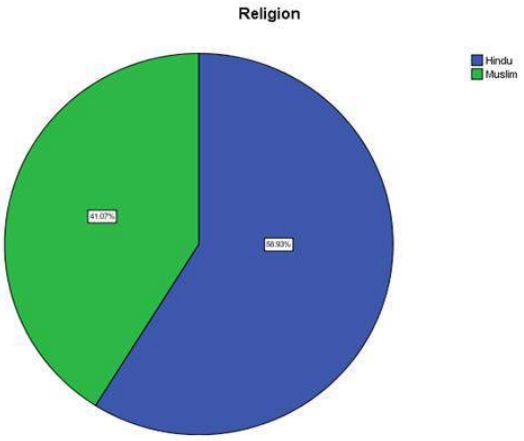


Figure2.

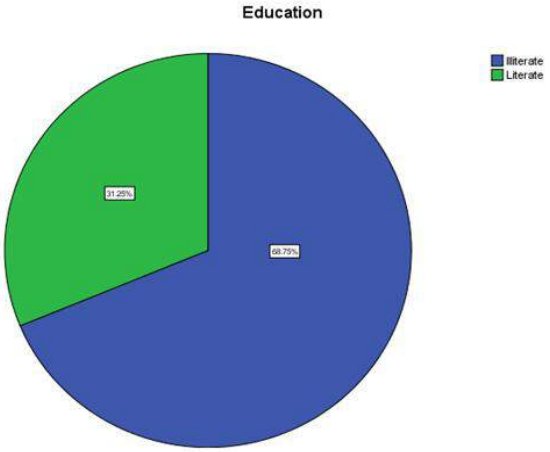


Figure3.

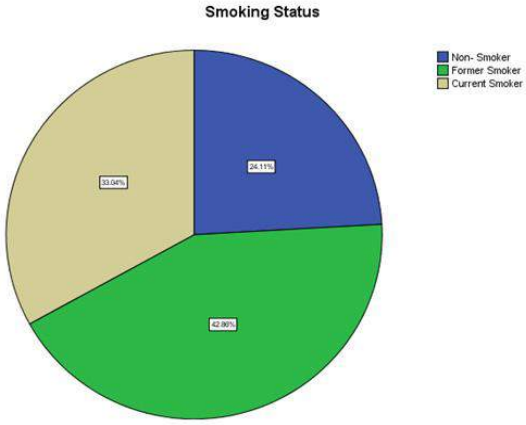
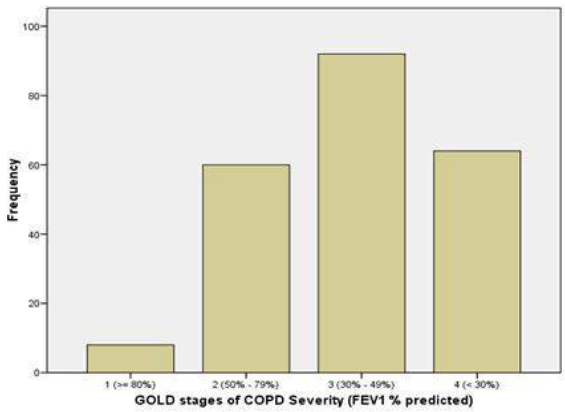


Figure4.



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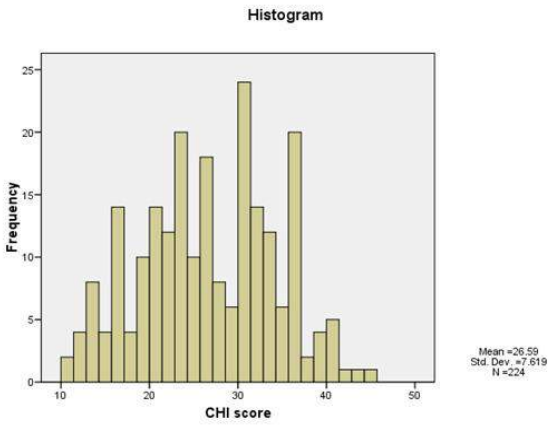

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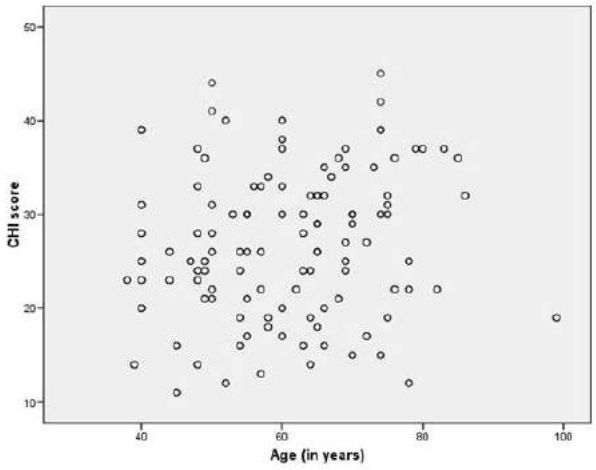

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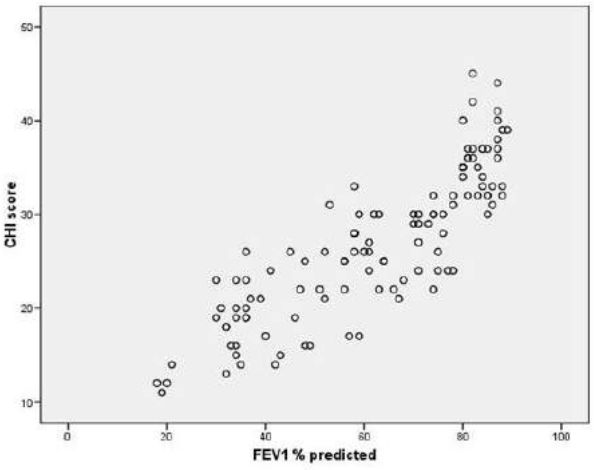

Figure8.

Age (in years)	Gender		Total
	Male	Female	
40 - 49	34	12	46
	19.3%	25.0%	20.5%
50 - 59	38	14	52
	21.6%	29.2%	23.2%
60 - 69	58	14	72
	33.0%	29.2%	32.1%
>= 70	46	8	54
	26.1%	16.7%	24.1%
Total	176	48	224
	100.0%	100.0%	100.0%

Table1.

GOLD stages of COPD Severity (FEV1 % predicted)

	Frequency	Percent
1 (>= 80%)	8	3.6
2 (50% - 79%)	60	26.8
3 (30% - 49%)	92	41.1
4 (< 30%)	64	28.6
Total	224	100.0

Table2.

Descriptives

CHI score

GOLD stages of COPD Severity	N	Mean	Std. Deviation	Maximum	Minimum	p-value
1 (>= 80%)	8	12.25	1.165	14	11	
2 (50% - 79%)	60	19.23	3.614	26	13	
3 (30% - 49%)	92	26.33	3.820	33	17	< 0.001
4 (< 30%)	64	35.66	3.277	45	30	
Total	224	26.59	7.619	45	11	

Table3.

Correlations

		Age (in years)	FEV1 % predicted	CHI score
Age (in years)	Pearson Correlation	1	.243	.157
	p-value		.000	.019
FEV1 % predicted	Pearson Correlation	.243	1	.856
	p-value	.000		.000
CHI score	Pearson Correlation	.157	.856	1
	p-value	.019	.000	

Table4.

Descriptives

CHI score

	N	Mean	Std. Deviation	Maximum	Minimum	p-value
Male	176	27.48	7.467	45	11	
Female	48	23.33	7.349	37	13	.001
Total	224	26.59	7.619	45	11	

Table5.

Descriptives

CHI score

Religion	N	Mean	Std. Deviation	Maximum	Minimum	p-value
Hindu	132	27.47	7.738	45	12	
Muslim	92	25.33	7.302	40	11	.038
Total	224	26.59	7.619	45	11	

Table6.

Descriptives

CHI score

Education	N	Mean	Std. Deviation	Maximum	Minimum	p-value
Illiterate	154	27.86	7.201	45	12	
Literate	70	23.80	7.820	37	11	< 0.001
Total	224	26.59	7.619	45	11	

Table7.

Descriptives

CHI score

Smoking Status	N	Mean	Std. Deviation	Maximum	Minimum	p-value
Non- Smoker	54	23.56	7.306	40	11	
Former Smoker	96	26.39	7.267	45	12	< 0.001
Current Smoker	74	29.07	7.533	44	14	
Total	224	26.59	7.619	45	11	

Table8.