Paan chewing: intergenerational habit transmission and lifetime dose-response relationship with oral cancer among a subset of South Indian population.

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DEDICATION

This work is dedicated to my parents Mr. Sankaran and Mrs. Sarawathi, and to my dear wife Anu for their unparalleled love, affection and support.

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LIST OF ABBREVIATIONS

IARC	International Agency for Research on Cancer
PCH	Paan Chewing Habit
PBI	Parental Bonding Instrument
RA	Research Assistant
AIC	Akaike's Information Criteria
MAR	Missing at Random
MICE	Multiple Imputation by Chained Equations
DAG	Directed Acyclic Graph
GATS	Global Adult Tobacco Survey
SEP	Socio Economic Position

ABSTRACT

Paan chewing habit (PCH) is highly prevalent in Asian populations, and the habit has been related to increased risk of developing oral cancer. Although several studies were conducted, little is known about two important aspects of this habit: intergenerational transmission and the associated dose-dependent risk. This thesis work pertains to investigations of these two important aspects of PCH.

Objectives: 1) To estimate the maternal and paternal contribution to the intergenerational psychosocial transmission of PCH among a subset of the South Indian population; 2) To estimate the dose-response relationship between lifetime cumulative exposure to paan chewing and risk of oral cancer using restricted cubic spline regression, in the same population.

Methods: In a hospital-based case-control study, the HeNCe Life study-India, incident cases (N=350) of oral squamous cell carcinoma were recruited from Government Dental and Medical College hospitals of Kozhikode, India. Non-cancer controls (N=371), frequency matched by age and sex, were recruited from different outpatient clinics of aforementioned hospitals. Data on socio-demographic and behavioural factors were collected using a questionnaire and life-grid technique.

Results: Maternal and paternal PCH were significantly associated with subject's PCH, with odds ratios (OR) of 2.40 (95% confidence interval (CI): 1.11–5.21) and 3.05 (95% CI: 1.48–6.27), respectively. The majority of the oral cancer cases had the habit of paan chewing (72%) compared to the controls (18%). A significant nonlinear dose-response relationship was observed between cumulative chew-years of paan and risk of oral cancer. There was no further increase in risk observed beyond 470 chew-years.

Conclusion: Parental PCH could be a component of the complex shared genetic and environmental factors that contribute to an individual's PCH. Multigenerational and culturally sensitive psycho-social intervention targeted towards families with PCH history should be considered for effective prevention of propagation of the habit through generations. More studies are needed to further understand the biological processes behind dose-dependent risk associated with PCH. The results may have implications for the development of effective paan cessation programs and individualized oral cancer risk assessment protocols.

RÉSUMÉ

L'habitude de chiquer du bétel et de la noix d'arec (*paan chewing habit*, PCH) est très répandue dans la population asiatique. Il a été démontré qu'elle augmente le risque de développer un cancer de la bouche. Toutefois, on connaît encore mal le rôle joué par la transmission intergénérationnelle et la relation dose-effet de cette habitude. Ce mémoire étudie ces deux aspects importants de la PCH.

Objectifs : 1) estimer les contributions du père et de la mère à la transmission psychosociale intergénérationnelle de la PCH dans une population du sud de l'Inde; 2) estimer la relation dose-effet entre le nombre d'années cumulées de la PCH (chique-années) et le risque de cancer de la bouche par une régression de spline cubique minimisante.

Méthodes : Dans une étude cas-témoin, la HeNCe Life Study- Inde, les cas incidents (n= 350) de carcinome spinocellulaire oral ont été recrutés dans les hôpitaux du *Government Dental and Medical College* à Kozhikode en Inde. Des témoins sans cancer (n= 371), appariés aux cas par âge et sexe, ont été recrutés dans différentes cliniques ambulatoires du *College*. Un questionnaire et une grille de vie ont été utilisés pour recueillir des informations sociodémographiques et les facteurs comportementaux.

Résultats: La PCH maternelle et paternelle étaient significativement associées à la PCH des sujets, avec des rapports de cotes de 2,40 (intervalle de confiance (IC) à 95% : 1,11-5,21) et de 3,05 (IC95% : 1,48-6,27) respectivement. La majorité des cas de cancer de la bouche avaient l'habitude de mastiquer du bétel et de la noix d'arec (72%) comparé aux témoins (18%). Une relation dose-effet non linéaire significative est apparue entre le nombre d'années cumulées de la PCH (chique-années) et le risque de cancer de la bouche. Aucune augmentation de risque n'était observée au-delà 470 chique-années.

Conclusion: La PCH des parents pourrait constituer un élément supplémentaire relatif aux facteurs génétiques et environnementaux qui contribuent à la PCH d'un individu. Des interventions psychosociales spécifiques pour les familles avec une histoire de PCH tenant compte des relations intergénérationnelles et de la culture devraient être envisagées afin de prévenir efficacement la propagation de cette habitude d'une génération à l'autre. D'autres études sont nécessaires pour mieux comprendre les processus biologiques sous-jacents à la relation dose-effet entre la PCH et le risque de cancer de la bouche. Les résultats pourraient favoriser le développement de programmes individualisés de cessation de la PCH et modifier les protocoles d'évaluation du risque de cancer de la bouche.

PREFACE

This work follows a manuscript based thesis style. As per McGill University standards, the manuscripts included in thesis should be logically-coherent and should have a unified theme. The two manuscripts compiled in this thesis work share the common theme of investigating two important stages of a habit known as paan chewing. The first manuscript discusses how the habit is transmitted through generations among South Indian families, and the second manuscript discusses how the habit is associated with risk of oral cancer in the generation to which the habit was transmitted. Additional texts and analysis are provided to connect the manuscripts and as part of the documentation of a single program of research. Following a brief introduction of the topic in the first chapter, current knowledge in the field is reviewed in the second. Supported by this knowledge base, the objectives of our study are discussed in the third chapter. Chapter four comprehensively discusses the methodology of the study, followed by the two manuscripts. The last chapter in this thesis discusses the methodological considerations, future research directions and conclusion of the study.

The manuscripts included in this thesis work have multiple authors; explicit appreciation of each author's contribution is mentioned next.

CONTRIBUTION OF AUTHORS

Manuscript #1:

Maternal and paternal contribution to intergenerational psychosocial transmission of paan chewing habit in South India

Sreenath Arekunnath Madathil, Master's Candidate: Conceived objective of the investigation, recruited participants, carried out statistical analysis and wrote the manuscript.

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Manuscript #2:

Dose response relationship between paan chewing habit & risk of oral cancer: Restricted cubic spline regression analysis

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1. INTRODUCTION

Paan chewing is an ancient habit with a history dating back thousands of years(1), yet still highly popular with more than 600 million users worldwide(2). Paan is a colloquial name for a mixture of four main ingredients: areca nut (nut of areca catechu tree), slaked lime (calcium hydroxide), betel leaf (leaf of the piper betel vine) and tobacco(1). The combination of this betel leaf, areca nut and slaked lime is also known as betel quid. The habit has been associated with increased risk of oral cancer for more than two decades and in 2003 the International Agency for Research on Cancer (IARC) classified betel quid with or without tobacco as a group 1 carcinogen(3).

From the perspective of public health intervention, there are two dimensions of paan chewing that are of particular importance: (i) how the habit is initiated; and (ii) how the risk associated with the habit changes depending on the pattern of consumption. While the former is important to design interventions targeted to individuals who are at risk for adopting the habit, the latter is important for developing individualized risk assessment protocols which could be used for behaviour modification counselling.

Through centuries, the habit of paan chewing has become highly intertwined with the culture of India to the extent that paan is offered as a token of respect for guests in family and religious functions(4,5). Hence, it is important to understand different dimensions of its value in the population for designing culturally sensitive targeted interventions.

This thesis explores these two dimensions of paan chewing by investigating the intergenerational psychosocial transmission of the habit and the dose-response relationship between the habit and risk of oral cancer in a subset of South Indian population.

2. LITERATURE REVIEW

The following section includes a comprehensive review of the literature on topics pertaining to oral cancer and its risk factors. Literature on each risk factor for oral cancer is reviewed independently, from a global as well as an Indian perspective, followed by details on its association with oral cancer. A special emphasis is given to the habit of paan chewing, its determinants, carcinogenicity and current evidence on its dose-response association with oral cancer.

2.1 Oral cancer – definition

A recent systematic review on the aetiology of oral cancer emphasized the need to adopt a standardized definition of the disease among investigators in the field(6). According to the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), oral cancer includes malignant neoplasms affecting the lip, tongue, gingiva, floor of mouth, palate, cheek mucosa, retromolar area and vestibule of mouth (ICD-10: C00-C06)(7).

2.1.1 History and epidemiology

The oldest documentation of cancer as a disease is believed to have been made around 1600BC in the Smith and the Ebers papyri; later in 460BC Hippocrates coined the term carcinoma(8). References to different forms of cancer can be found in many medical writings of different civilizations. In India, the oldest reference to oral cancer can be found in *Sushrutasamhitha*, an ancient medical manual in the Indian system of medicine - Ayurveda. This ancient manuscript is believed to have been written around 3rd of 4th century BC by Sushrutha, an Indian scholar known as the father of surgery. He mentioned it as Mukharbuda, and classified it into two groups: Granthi (minor neoplasm) and Arbuda (major neoplasm)(9).

The latest available global epidemiological data shows that cancer of the lip and oral cavity is among the 15 most prevalent cancers globally, with above 2.6 million new cases diagnosed in 2008(10). The majority (90%) of them are squamous cell carcinomas and most are seen between the 5th and 7th decades of life(11).

However, recent population studies show a trend of increasing incidence among young individuals (<40 yrs of age); especially in the developed nations(12,13). Globally, the highest age standardized incidence rate is reported in Melanesia (17.8 per 100,000) followed by South-Central Asia (7.4 per 100,000) regions (14). Most of these cancers are due to high exposure to major risk factors such as tobacco and alcohol. Among different countries worldwide, India has the 10th highest age standardized incidence rate (7.5 per 100,000), and a mortality rate of 5.2 per 100,000(14). It is the second and fourth most common fatal cancer among Indian men and women aged 30 to 69 years, respectively (15).

Despite the advances in treatment options, the five-year survival rate of oral cancer is only around 50% in many countries, and it has not improved for past several years(16). In 2010, the age standardised mortality of this cancer in India was 22.1 and 9.4 per 100,000 among men and women, respectively(15). This number is predicted to rise with an estimation of more than two million new cases by 2020(17).

2.2 Risk factors of oral cancer

Since the time of Sushrutha, oral cancer risk factors have been widely studied. According to him, cancer was caused by pathogenic injuries to the sixth layer of skin called 'Rohini' (epithelium). These pathogenic injuries include lifestyle errors, bad habits, poor hygiene, and unhealthy foods(9,18). Even after more than 1000 years, these remain the major oral cancer risk factors studied. In the current literature, the main identified risk factors for oral cancer include tobacco (smoked and smokeless), alcohol consumption, betel quid or paan chewing, diet low in fruits and vegetables, low socioeconomic position, poor oral health status (number of missing teeth, periodontal infection), constant mechanical irritation (ill-fitting denture or sharp teeth), human papillomavirus infection, diseases of the oral mucosa (pre-malignant conditions)(6). Other less studied risk factors are Epstein bar virus infection(19), family history of cancer, use of mouthwash containing alcohol(20), occupational exposures and oral microbes(21).

In the following section, we briefly discuss the major risk factors for oral cancer. In most parts of Asia, the habit of paan chewing is one of the major risk factor for oral cancer. In India alone, 42% of oral cancer incidence among men and 81% among women is attributed to this habit(22). Hence, a special emphasis is given to the current knowledge on the epidemiology, determinants of paan chewing and its association with oral cancer.

2.2.1 Smoked tobacco

Smoking tobacco in different forms has been associated with oral cancer. The most common form of smoked tobacco worldwide is cigarette. The prevalence of smoked tobacco in India is around 14% and most users are current daily smokers. In India, the habit is more prevalent among males (24%) compared to females (3%)(23). Smoked forms of tobacco in India include cigarette, bidi, hookah, pipe, cigar, and some other forms, such as chutta and chillum(23). Literature pertaining to the three major forms of smoked tobacco is reviewed below.

Cigarette smoking

The global prevalence of cigarette smoking is around 1.25 million. Most of this global burden is in developing countries with 50% of men and 9% of women smoking compared to 35% of men and 22% of women in developed countries(24).

The association between cigarette smoking and oral cancer was established by an international working group of experts in 1985; since then, many studies have investigated different aspects of this association(25). The oral cavity is believed to be less sensitive to smoked tobacco compared to the larynx and other parts of the upper aerodigestive tract. A significant dose-response relationship has also been established between intensity, duration and pack years of cigarette smoking and oral cancer(26). The risk has shown to reduce after cessation of smoking reaching similar risk as a non-smoker after 10 or more years of cessation(26).

Cigarette smoking is the second most common type of smoked tobacco in India with a prevalence of 6%. Contrary to international studies, research from India shows little or no association between filtered cigarette smoking and oral cancer(27). This could be due to the high prevalence of an indigenous variety of cigarette called bidi and the chemical difference between the smokes produced by two types of cigarettes.

Bidi smoking

Bidi is the indigenous form of smoked tobacco, particular to the Indian sub-continent. It is made by hand rolling 0.2 to 0.5 grams of raw tobacco into a dried *tendu* leaf (*Diospyrusmebunoxylon or Diospyrusebenum*) and securing it with a thread at one end.

Bidi remains the most popular variety of smoked tobacco in India; 9% of Indian adults have ever smoked bidi in their life. The majority of them (81%) are current daily smokers. Bidi smoking is more prevalent in rural areas, whereas cigarette smoking is more common in cities(23). Bidi has a greater concentration of nicotine and tar than cigarettes, and due to its unfiltered nature more carbon monoxide is also inhaled when smoking bidi. In a pooled analysis, Rahman et al reported a threefold increase in risk for oral cancer among bidi smokers compared to non-smokers, and the risk increased with frequency of use and lower age of initiation(28). Recent cohort study results from southern India suggested a fivefold increase in risk of oral cancer for bidi smokers among men, whereas no risk was associated with cigarette smoking(29). Risk augmentation has also been reported with concomitant use of betel quid or alcohol(22,30,31).

Hookah and Marijuana smoking

Water pipe (hookah, shisha) smoking is a popular smoked tobacco habit in the Eastern Mediterranean, Middle East and some parts of Asia(26). Recent studies show the rising trend in its prevalence in the western world(32,33). Ward et al reported that there are more than 100 million hookah users worldwide(34). Hookah smoking is the third most prevalent form of smoked tobacco in India with around 7,100 thousand ever users(23).

Although the habit has been associated with an increased risk of lung cancer, oesophageal cancer(35,36) and periodontal disease(37), only a few studies have investigated its association with oral cancers and the results are inconclusive due to confounding by other factors(38).

Marijuana (*Cannabis sativa*) is the most widely used illicit drug in the world, and its use is increasing among adolescents(39). Marijuana use often co-occurs with smoking, alcohol abuse and other drug abuse. Since cannabis smoke contains carbon monoxide and polycyclic aromatic hydrocarbon, it has been investigated as a carcinogen for humans. However, studies have failed to identify an association between oral cancer and cannabis use(40,41). Conversely, cannabinoids present in marijuana have been shown to have health benefits including antineoplastic activity, but more studies are needed to obtain a conclusive result(42).

2.2.2Alcohol consumption

IARC reports a global average per capita of pure alcohol consumption of 6.2 litres in 2002. More than half of men (55%) and one third of women (34.4%) consume some form of alcoholic beverage globally. The consumption is the lowest in Muslim and Eastern Mediterranean countries and the highest in Eastern European countries with a per capita consumption of 13.9litres per year (43–45).

A sharp rise of 8% in alcohol consumption was reported in India between 2006 and 2009. As in the case of smoking, alcohol consumption is more prevalent among men (21%) than women (2%) in India(46). In a population study conducted in Southern India, the average age of starting of this habit was 13years old among men(46).

Alcohol was established as an aetiological factor for oral and pharyngeal cancer by IARC in 1988. Cohort studies have reported a relative risk for oral cancer ranging from 3.5 to 9.2 associated with the habit of alcohol consumption, with a strong dose-response relationship(44). Effect measure modification has been reported among tobacco smokers and betel quid chewers, among whom the combined effects were multiplicative(31).

2.2.3 Socioeconomic position (SEP)

SEP has been defined as the socially derived economic position an individual holds in a multiple-stratified structure of society(47). This position may be influenced by many factors that are interlinked. Some of these factors are social class, economic situation and life chances created by exchange of skills, education or social influence(47,48). Many chronic diseases are socially patterned, where some diseases are concentrated among those with high SEP (e.g., melanoma)(49,50) and some among those with low SEP (e.g., mortality rate of breast cancer)(51). Exposures also follow a socioeconomic gradient, so it is important to measure and adjust for individuals' socioeconomic circumstances to avoid confounding. SEP is measured through different indicators, among which income, education, occupational status and housing conditions are the most common. In our study, education and housing conditions were used as indicators of participant's SEP, hence current knowledge on these indicators are reviewed below.

2.2.3.1 Education

Level of education is a commonly used indicator of SEP because of its ease of measurement and its ability to capture individuals' knowledge related assets(52). Education level is also highly correlated to parents' SEP and their choices, social opportunities and access. Moreover, education is a strong predictor of future employment, especially in industrialized countries(47).

The same level of education could have a different meaning and impact on individuals' life depending on the age, period and cohort, so it may be difficult to directly compare the effect of this variable between different studies.

2.2.3.2 Housing conditions

Housing conditions indicate the wealth that an individual has accumulated over a period(52). Usual measures of housing conditions are tenure (owned/rented), amenities (e.g., access to hot water, availability of toilet, telephone, refrigerator,

and car) and materials (e.g., building material, type of flooring, number of rooms)(52). As a whole, this indicator measures material circumstances.

2.2.3.3 Association between SEP and oral cancer

A systematic review by Conway et al reported almost two fold increases in risk for developing oral cancer associated with low education attainment, low occupational social class and low household income(53). Several possible pathways through which SEP factors directly or indirectly increase this risk have been proposed such as increased risk taking behaviours leading to adoption of habits, poor access to health care, and accumulated work stress(54). Moreover, a previous analysis from our own research group showed a strong gradient of oral cancer risk across the life course; the risk increased with an increasing time spent in low SEP. Even after adjusting for other known risk factors, a fourfold increase in risk was reported for participants who remained in low SEP compared to those who remained in high SEP throughout their life(55).

2.2.4 Human papillomavirus

Papillomaviruses are small circular double stranded DNA viruses. There are more than 120 types which can affect humans, collectively called human papillomaviruses (HPV)(56). These viruses are known to cause a range of diseases from common warts to cancers and cardiovascular disease(57). HPV infection was established as risk factor for cervical cancer by IARC in 1995(58), moreover their 2007 and 2012 reviews confirmed that there is sufficient evidence for establishing HPV infection as a risk factor for oropharyngeal cancers(59).

The modes of HPV infection and transmission are believed to be through unprotected sexual behaviours or vertically from an infected mother to her child during birth(56). Increased frequency of oral sex, early life initiation of sexual activity and a high number of sexual partners have been associated with an increased risk of HPV infection(60).

The global prevalence of cervical HPV infection is 6-40% among women(59), however it is estimated that latent infection could be found in 10-12% of

clinically healthy oral mucosa(61). The prevalence of HPV is 5-10 folds lower in the oral cavity than in the cervix.

The most common types of oral HPV are HPV- 6, 11, 16, 18, 31, 33 and 42. In a meta-analysis including 60 studies the overall prevalence of HPV in oral cancer was 23.5%(62). HPV-16 was the type most commonly associated with oral cancer (68.2% of HPV positive oral cancers)(62). The floor of mouth and tongue are the most common sites associated with HPV-16 positive oral cancers(63).

2.2.5 Diet

It is estimated that 30% of human cancers are attributable to dietary intake and nutritional deficiencies in developed countries(64), and 20% in developing countries(65). In the field of head and neck cancers (H&NC), individual food products and diet patterns have been widely investigated. A recent systematic review noted inconsistencies in the associations reported in studies from different parts of the world(66). Diet is highly related to the history, culture, climate and geographical position of a population and it would be difficult, even inapplicable to pool the results from studies conducted in different parts of the world. However in general, a Mediterranean diet(67) and diets rich in vegetables and fruits(68,69) have been proposed to have a negative association (protective effect) with H&NC. Conversely, diets low in vitamins, fibres and unsaturated fats have been shown to increase the risk of H&NC(70).

An epidemiological study from India showed a 39% increase in oral cancer risk among non-vegetarians compared to vegetarians(71). In addition to the above mentioned food components, studies from Southern India also showed a significant reduction of oral cancer risk associated with an increased intake of dairy, fish, eggs, citrus fruits and pulses(72). However, an increased risk was noted with the consumption of red chillies, the cereal ragi, ham and salami(72).

2.2.6 Other risk factors

In addition to the known risk factors described above, several other exposures are considered in the literature as potential risk factors for oral cancer. Many of these associations are only in the early stages of investigation.

2.2.6.1 Oral health related factors

Periodontal disease is the chronic inflammatory disease of the periodontium. The possible inflammatory pathway of carcinogenesis motivated several investigators to study the association between periodontal disease and oral cancer. The most commonly employed measures of periodontal disease in these studies are chronic periodontitis, alveolar bone loss, gingival pocket depth and degree of attachment loss. Tezal et al reported an approximately five-fold increase in the risk of tongue cancer associated with each millimetre of alveolar bone loss, even after adjusting for other known risk factors(73). Poor oral hygiene, inadequate or infrequent brushing, missing teeth and wearing ill-fitting dentures have been shown to significantly increase the risk of oral cancer(74–76), whereas regular visits to a dentist reduced this risk(77). However, more studies are needed to clarify and confirm these associations.

2.2.6.2 Oral microbes

Different oral bacteria have been suggested to play a role in the development of oral cancers. *Streptococcus anginosus* and *Treponema denticola* have been associated with esophageal cancers(78). Although unclear, some of the commonly proposed mechanisms by which they act are through the induction of cellular proliferation, an interference in cellular signalling mechanisms, the inhibition of apoptosis and the high metabolism of carcinogenic acetaldehyde in alcohol consumers(79,80).

Some oral conditions such as Candidal leukoplakia, caused by *Candida albicans,* have been shown to undergo metastatic changes in 9-40% of cases(81). However, a recent review identifies contradictions in the current evidence and calls for further studies(61).

2.3 Paan chewing habit

Paan chewing is the colloquial term for habitual chewing of betel quid with tobacco, which is very popular in many South and South-East Asian countries(82). The following section will describe the literature on ingredients, preparation and usage and chemical constituents of paan. In addition, we review the epidemiology as well as the main determinants of paan chewing.

2.3.1 A brief history of paan chewing

Paan chewing is an ancient habit dating back more than 2000 years. The origin of this habit is debatable, although literary evidence strongly favours the theory of an Indian origin; linguistic evidence proposes that it originated in Indonesia. Moreover, the discovery of areca nut remains, dating back to 10,000 BC, in the Spirit caves of Thailand supports the second theory(1). In addition, skeletal remains excavated form Nui Nap in Northern Vietnam showed areca nut residues on dentition, proving the existence of the habit as early as the Bronze Age in this region(83). Literary evidence of existence of the habit on Indian sub-continent dates back to the *Vedic period* (2000-500 BC). Tobacco is not indigenous to India, therefore paan did not include tobacco before its introduction by Europeans around 1600 BC(84).

2.3.2 Paan – Ingredients

The habit of paan chewing has a wide documented geographical distribution from Melanesia in the east to the eastern coast of Africa in the west and from Southern China in the north to Papua New Guinea in the south(1). Through the long history of this habit, its ingredients, preparation and usage have evolved and adapted to the availability of raw materials in their respective geographical areas. The IARC in its recent monograph on personal habits and indoor combustions has published a comprehensive list of common ingredients of paan according to countries of usage(85). Paan, in its basic form, includes three ingredients: betel leaf, areca nut and slaked lime; users in many parts of the world generally add tobacco to this combination(82).

Betel leaf

Betel leaf is the leaf of a perennial vine of the *Piperaceae* family called *Piper betel*. Betel leaf is cultivated mainly in tropical climates and is used as fresh unripe or ripe leaf. As a common norm based on cultural beliefs, the veins and the tip of the leaf are removed before chewing(1). Chemical studies on betel leaf show that it contains different phenol compounds such as hydroxychevico, euginol, phenol, chevicol and trace amounts of vitamin C(85). A few *in vitro* and *in vivo* studies have shown the anti-bacterial, anti-fertility, anti-carcinogenic, anti-oxidant and anti–haemolytic activities that supports its use in Indian traditional medicine (*Ayurveda*)(86,87).

Areca nut

The areca nut, sometimes wrongly identified as betel nut in Western literature, is the nut of a palm tree (*Areca catechu*) abundantly seen in tropical regions(1). Different forms of processing exist for areca nut, some of which are raw or ripe use, sun drying, boiling in water, roasting, adding fragrance with spices, boiling with *benzoin*, and less commonly aging the nut in salt(1,5).

Biochemical studies have identified four major alkaloids in areca nut: Arecoline (1,2,4,5-tetrahydro-l-methyl-pyridinecarboxylicacid), arecaidine (1,2,5,6-tetrahydro-l-methyl-3-pyridinecarboxylic acid), guvacine and guvacoline. The concentration of these alkaloids may vary depending on the geographical area and the processing technique(88). Areca nut is considered to be the fourth most prevalent psychoactive substance in the world after caffeine, alcohol and nicotine(82), and studies have shown the addictive capacity of the areca nut even without tobacco(89).

Slaked lime

Slaked lime is a thick paste of calcium hydroxide obtained from sea shells or limestone depositions according to geographical availability(85). In some parts of South-East Asia, turmeric or other spices are added to slaked lime to give it a fragrance or pink color(1).

Smokeless tobacco

Different forms of smokeless tobacco are used along with betel quid. More prevalent forms are sun or air cured, processed and manufactured. The cheapest form of tobacco is sold as unprocessed bundles of tobacco leaves and powdered sticks. Gupta et al reviewed different forms of smokeless tobacco use in India and South Asia and found that it is the major (40%) form of tobacco consumption among Indians. Most smokeless tobacco is of the species *Nicotiana rustica* which has higher concentrations of nicotine than the most common smoked variety (*Nicotiana tabacum*)(84).

Supplementary ingredients

According to personal preferences and availability, supplementary ingredients such as cardamom, anise seed, clove, camphor, musk, nutmeg, copra, black pepper, dry ginger and sweetening agents are also included in paan. Gambier, an extract from the *Uncaria gambir* plant, is a common supplementary addition in Malaysia, whereas a reddish brown extract form *Acacia catechu* or *Acacia Suma* called Catechu is commonly added in many parts of India(82).

2.3.3 Preparation and usage of paan

In the typical preparation and usage of paan, the slaked lime is smeared on to the betel leaf which is then used to wrap slices of areca nut and tobacco to shape it into a triangular portion referred to as a quid. The quid is then placed between posterior teeth and chewed on. The masticatory action produces a red coloured liquid which is swallowed or spat out(1). Other forms of usage have also been documented, some of them are:

- Chewing the betel leaf smeared with slaked lime and then taking other ingredients one by one.
- Rubbing the quid on to the anterior teeth vigorously to shred it and then chewing.
- Pounding the hard to chew quid to a smooth mixture and then chewing it.

2.3.4 Epidemiology of paan chewing

There are approximately 600 million paan users worldwide(2), but most of them are concentrated in the South and South-East Asia and Pacific Islands. Prevalence of this habit has also been shown among immigrant populations of Africa, Europe and North America including Canada(90). It is difficult to estimate the global prevalence of paan chewing because of the diversity of ingredients used, for example, tobacco is never combined with betel quid in Southern China, Taiwan and Papua New Guinea, whereas they are combined in most parts of the Indian subcontinent(2). However, Gupta et al estimated a global prevalence of paan based on areca nut usage as 10-20%(2). The Asian betel quid consortium recently reported the trends in habit prevalence in South and South-East Asia. Although the habit is dying in Cambodia, Indonesia, Thailand and Vietnam, a rapid increase has been noted in India, Taiwan and China with a prevalence as high as 70-80% in Palauans of the West Pacific(90).

2.3.4.1 Indian perspective

Paan in India almost always contains tobacco. Therefore, many researchers classify it under the title of smokeless tobacco. The 2009-2010 Global Adult Tobacco Survey (23) is the latest available population prevalence data on smoked and smokeless tobacco use in India. More than one fourth of the population consumes some form of smokeless tobacco. There are 170.2 million daily users and 35.8 million occasional users. The habit is more prevalent among males (33%) compared to females (18%), and in rural areas (30%) compared to urban areas (17%). Smokeless tobacco use also shows a strong socioeconomic gradient: the higher the education attainment, the lower the prevalence of the habit. The prevalence of use also varies by geographical area; the province of Bihar has the highest prevalence rate at 49%, and the lowest is in Goa with 5%. The most prevalent form of smokeless tobacco is Khaini, which is a mixture of tobacco and lime, followed by the combination of betel quid and tobacco.

The quitting ratio of smokeless tobacco is very low (5%), and it does not differ by sex or SEP(23). The tobacco-related mortality rate in India is expected to rise to 1.5 million annually by 2020(91). The direct medical cost related to smokeless tobacco use was around 285 million in 2004, and this number is expected to rise(92).

2.3.5 Age at initiation of paan chewing

The Indian 2009-2010 Global Adult Tobacco Survey reported that among ever daily users of paan ages 20-34, 16% started the habit by 15years of age, and the mean age of initiation was 17.9 years(23). On an average females started at a younger age (17.9 years) compare to males (18.2 years). About 26% of women started the habit below 15 years of age compared to 12% of men. About 57% of male and 60% of females started the habit before 20 years of age(23). This early age at initiation is alarming and many studies have looked into the determinants of this phenomenon.

2.3.6 Socio-cultural determinants of paan chewing initiation

A recent systematic review on the social context of smokeless tobacco use compiled different socio-cultural reasons for commencement of this habit in the South Asian population. The reasons included cultural and social acceptance, peer and family pressure, the low cost of the product, mental relaxation, misunderstood medicinal properties and improved concentration(93). Studies have also reported that the easy availability of the product, SEP, smoking and alcohol consumption are determinant factors for commencement of paan chewing(94–96). The most common social context reported by studies was paan use by family members, the reported prevalence of the habit among family members ranging from 59% to 100%(93). Bangladeshi immigrant families reported that 81% of teenagers used betel quid which was readily available at home because of their parents' habit(97).

2.3.6.1 Intergenerational psychosocial transmission of paan chewing

The intergenerational continuity of substance use and misuse has been widely studied in the field of smoking(98–100), alcohol consumption(101–103) and other drug abuse(104). Paan chewing is a similar deleterious habit that has been proven to develop dependence among its users(89,105). Yet, very few studies have investigated the association between parents' and their children's paan chewing habit (106–108). All of these studies were cross-sectional surveys done among adolescents or school children; two of them investigated the habit of areca nut chewing(106,107) and the third examined smokeless tobacco(108). El-Amin et al reported that if one of the parents had the habit of smokeless tobacco chewing, the risk that their children would also start the habit was 1.77 times higher as compared to children whose parents did not have this habit(108). The studies on areca nut used simple chi-square tests, did not adjust for potential confounders, and only reported prevalence rates. Both of them reported a significant correlation between parents' areca nut chewing habit and their children. The sex of the parent has an effect in the intergenerational transfer of smoking(109), but this variable has not been investigated in regards to the habit of paan chewing. Moreover, no studies have quantified the parental influence on children's commencement of paan chewing.

The parent–child interaction patterns may highly depend on the psychosocial relationship between them. The significance of this relationship in intergenerational continuity of behaviours is discussed below.

2.3.6.2 Parenting styles and intergenerational continuity of behaviours

Relationship with parents and family experiences play an important role in moulding the personality of a child. An important part of this childhood experience is influenced by child rearing practices or, in other words, parenting styles. The seminal work by Baumrind on parenting styles identified three different styles; authoritarian, authoritative and permissive(110). Maccoby and Martin in 1983 modified this model (111) and redefined the permissive style to two slightly different styles: neglectful and indulgent.

Child rearing practices have been strongly associated with children's relationships with peers and authority, academic achievement, delinquency and substance abuse(112). Moreover, parenting styles seem to have an important role in the intergenerational transmission of smoking(113,114) and alcohol(102,115,116). An authoritative parenting style, which is supportive and flexible, allowing the expression of the child's feelings, has the most protective effect against adolescent smoking, alcoholism and substance abuse(117). Conversely, a neglectful parenting style, which is being indifferent to the child, imposing no rules or punishment and having low expectations from the child, is shown to be a risk factor for adolescent substance abuse(118).

There are two perceptions of parental bonding or parent child relationship: the child's perception of how well they bonded with their parents and the parent's own perception; these could be different. Studies show that the former is more important than the latter in predicting risk taking behaviours and delinquency(119).

Measuring parenting styles

Scholars have used different instruments to measure parenting styles. The Parental Bonding Instrument (PBI) by Parker et al(120) is the most consistently used instrument(121). PBI is a 25 item self-reported questionnaire based instrument which captures two perceived parenting styles – care and over protection. The participant completes PBI, one for each parent, as they remember them in the first 16 years of their life. The instrument has shown to be reliable (122,123) and stable(124) over long periods of time and not affected by sex of the respondent or their social class, however it is sensitive to cultural influences(125). Moreover, PBI has been shown to be insensitive to the current psychological makeup of the respondent(126,127), hence it is ideal for measuring retrospective data on perceived parental bonding from patients in high distress like cancer patients.

Although research supports the importance of parent-child relationship in the intergenerational transmission of substance abuse, none have studied this effect in the habit of paan chewing. Moreover, it would be particularly important in an Indian context considering the differences in socially accepted norms for child rearing practices(128).

2.3.7 Measuring paan chewing

Paan is usually consumed as quids (a substance or mixture of substance which is kept in mouth or chewed). Widely used measures of habit are age of initiation or commencement of habit, age of cessation of habit, average frequency of usage, most commonly used type of paan (particular combination)(85). Less frequently, information on the time that the substance is kept in mouth is also measured. Although this array of measurements provides an illusion of robust measures, most of the previous studies which used retrospective data, collected these measures as an average lifetime value, as recalled by the participant. This method increases the probability of incorporating considerable measurement errors in to the data. For example, the duration of the habit of paan chewing is most often computed as the difference between age at initiation and age at cessation of habit, this method ignores the possibility of the participant having an intermediate period in which they stopped the habit. Depending on the length of this intermediate period, the computed duration would be erroneous. Moreover, while investigating diseases with long latency periods such as oral cancer, it is important to measure changes in the habit throughout participants' lives because patient reported onetime measure (average) will be highly correlated to the current status, which may or may not be associated with the disease.

2.3.8 Association between paan chewing and oral cancer

Dr. W C Bentall's report on 'Cancer in Travancore, South India' in 1908 is one of the earliest documentations of a plausible association between paan chewing and oral cancer in India(129). His detailed account of ingredients, preparation and use of paan further provides the evidence of an unchanged practice of paan chewing for more than 100 years in that part of the world.

Since Bentall's report, several studies have investigated the carcinogenic potential of paan independently and in combination with other risk factors. IARC first evaluated the carcinogenicity of betel quid in 1984, and in 2004 they classified betel quid with or without tobacco as well as areca nut alone, as group 1human carcinogens(3). The reported relative risk associated with the habit shows a wide variation, from 1.5 to 58.4 for betel quid without tobacco and from 0.7 to 45.9 with tobacco. This could be due to variations in types and processing techniques of tobacco, areca nut and betel leaf among studies, which may affect the carcinogenic potential of the ingredients(85). A recent systematic review on risk factors for oral cancer reported a two fold increase in risk when betel quid was used in combination with tobacco compared to betel quid without tobacco. Risk increased according to the frequency and duration of chewing, early initiation of the habit and overnight keeping of the quid in the mouth(6). Squamous cell carcinoma of the buccal mucosa is the most common oral cancer associated with this habit, followed by cancers of the gingiva, tongue, and floor of mouth(6).

Several studies have investigated the interaction between paan chewing and multiple habits such as smoking and alcohol consumption, and reported a sub-multiplicative interaction effect with smoking and a multiplicative interaction with alcohol consumption(85).

2.3.9 Molecular and genetic carcinogenic effects of paan chewing

Systematic reviews on carcinogenic pathways of paan chewing show that its effects occur on multiple levels: cellular, extracellular and genetic. The major pathways of carcinogenesis due to paan chewing are an alteration of the genetic environment through accumulation of mutations, matrix metalloprotien modulation and down-regulation of its tissue inhibitors(130), and oxidative damage through generation of reactive oxygen species(85,131). Genetic susceptibility has also been reported in populations with high prevalence of the habit; polymorphisms in DNA repair genes XRCC1 & XPD among Indians and XRCC4 among Taiwanese, and polymorphisms in phase-II detoxifying enzyme encoding genes such as GSTT1 & GSTM1 among Indians and CYP2A6 among

Sri-Lankans have been associated with an increased risk of H&NC including oral cancer(132–134).

2.3.10 Dose-response relationship between paan chewing and oral cancer

According to Bradford Hill's criteria for causality, a dose-response relationship is an important criterion when considering whether a relation is causal(135). In addition, identifying how cancer risk changes according to the dose of the carcinogen could be valuable in risk assessment and for the development of effective prevention strategies.

Several studies have shown a significant increasing trend of oral cancer risk associated with increases in duration, daily amount, and cumulative exposure of paan chewing(22,30,31,136,137). A trend of reducing risk with increase in age at initiation of paan chewing and years since quitting has also been reported(29,30,138). Most of the studies investigating a dose-response relationship between paan chewing and oral cancer adopted a trend analysis, a method known for its limitations. Details of trend analysis, its limitations and proposed alternatives are discussed below.

2.3.10.1 Statistical techniques for assessing dose-response associations

Trend analysis

Trend analysis is the most widely used method of assessing dose-response associations for continuous exposures such as smoking, alcohol and occupational exposure levels. It is performed by first categorizing the continuous variable and then testing for a trend in the effect measures obtained for each category from a multivariate model, usually regression. However, trend analysis could be misleading as it does not necessarily imply a monotonic relationship(139). Moreover, the categorization of the continuous exposure increases the number of parameters in the model, thus reducing the power(140). Also, the cut-off points chosen for categorization can influence the results because of erroneous imposing of linearity in each category. In other words, the model assumes that the response remains constant within each category and can only change between categories.

This assumption results in a sudden jump in the effect measure or risk at the intersection of two categories that is rarely seen in natural situations. These shortcomings have been noted previously and more flexible alternative models have been proposed to overcome them(141). A strict linear dose-response relation is rare in natural settings, and flexible models are more efficient in modeling non-linear dose-response associations and provide more realistic results; spline regression is one of them(142).

Restricted cubic spline regression (RCS) - a flexible alternative

Spline regressions are piecewise polynomial regressions of degree *n* which are continuous at each cut point, called knots(143). A cubic spline regression is a spline model with n=3. One of the shortcomings of spline models are their sensitivity to outliers, thus the interpretation at the tails of the dose-response curve becomes difficult. Restricted spline circumvents this disadvantage by imposing linearity at the first and last segments(144). Hence, restricted spline regression will have at least three knots or four segments, to allow sufficient flexibility. Since the shape of the dose-response curve may depend on the number of knots and not their position, different models with varying numbers of knots could be tested to determine the best fitting model; for exploratory analysis, three to seven knot models are usually tested(145). Akaike's information criterion (AIC) is commonly used to select the model providing the best fit among these; the one with the lowest AIC value is chosen(146).

Recently, RCS has been used to estimate the dose-response curve of risk of oral cancer to intensity of smoking and alcohol consumption(147,148). However, no studies have utilised the potential of RCS in exploring the dose-response relationship of paan chewing habit with oral cancer.

In summary, although there is a huge body of literature pertaining to the habit of paan chewing, considerable knowledge gaps exists in the areas of transmission of the habit through generations and dose-response relationship between the habit and oral cancer. Addressing these knowledge gaps are essential as they pertain to two major points in the habit trajectory, intervening on which will have significant public health impact.

Firstly, better knowledge of the factors related to initiation of paan chewing will allow interventions to be directed towards breaking the intergenerational continuity. Secondly, through the identification of high risk populations based on the habit trajectory over time, interventions may be optimally targeted towards risk reduction.

The current project was designed to address these knowledge gaps.

2.4 Source population

The study was conducted in Kerala, a Southern province of India with a population of more than 30 million and the highest literacy rate in the country (94%)(149). A recent survey reported that 11% of the Kerala population are current users of paan, which is below the national average of 26%. Approximately 7% of this population are daily users and 87% never used paan. The habit is more prevalent among males (18%) compared to females (9%). Betel quid with tobacco is the most prevalent form of paan used, with 9% of males and 7% females as current users. Among ever daily users of paan aged 20-34, 16% of them started the habit before 15 years of age and 34% before 20years(23). National cancer registry program reports an age standardized incidence rate of oral cancers excluding tongue cancer in Kerala, as 7.1 per 100,000 among males and 4.4 per 100,000 among females. The age standardized incidence rate of tongue cancer was 5.0 and 2.7 per 100,000 among males and females respectively(150). Due to the above mentioned facts Kerala was chosen as the site for investigating our research questions.

3. RATIONALE

Oral cancer is a severe debilitating disease which affects more than two million people each year around the world(14). Paan chewing is a major risk factor for oral cancers in South Asia. This habit, known to mankind for many centuries, has been associated with oral cancer for several decades. In spite of many public health initiatives to increase awareness among the general population, the prevalence of this habit is rising in India(90).

From the public health perspective, probably the two most important intervention approaches are through (i) increasing awareness among those who do not have the habit and thereby preventing them from acquiring it; (ii) motivating those who have the habit to refrain from it. From an Indian context, both of these approaches have built in challenges.

Commencement of paan chewing usually occurs in the early stages of life; a recent survey from India reported that more than one third of the current users of paan started the habit before 18 years of age(23). At this early age, it is difficult to make an informed choice between a future probability of health consequences due to the habit and the momentary pleasure of indulging in it. Eventually, depending on external influences, the decision pendulum can slant towards either choice. Therefore, it is very important to study these external forces. A recent systematic review reported that along with peer influence, the habit of a family member is a strong determinant of the commencement of paan chewing(93). Moreover, one of the most common social contexts of paan use was the use by a family member. These findings warrant the investigation of how the paan chewing habit is transmitted within families. The intergenerational transmission of behaviours is widely investigated in smoking, alcohol consumption and other drug abuse, yet very few studies have investigated this phenomenon with regards to paan chewing. Moreover, all of them have conceptual and analytical weaknesses. The socio-cultural aspects of Indian society make this question particularly relevant to it. Unlike smoking or alcohol consumption, paan chewing is socially valued and it is based on religious and cultural practices. Yet, none of the previous studies have

investigated the intergenerational psychosocial transmission of paan chewing in Indian families.

Parent-child bonding has a strong modifying effect on the intergenerational transmission of smoking and alcohol habits. This modification effect could be highly important in an interdependent society such as India, where the parenting styles are different from those in the Western world, but no previous study has explored this aspect in relation to paan chewing. It is essential to understand the intergenerational transmission of paan chewing and the factors that modify it for the development of multigenerational, culturally sensitive interventions and the effective implementation of those interventions. Our study (manuscript I) addresses this knowledge gap by investigating the association between participant's and their parents' paan chewing habit. Moreover, we explore how the participant's perceived relationship with each parent plays a role in this association.

The second approach for intervention is among current paan chewers. In India, since paan most often contains tobacco, interventions against paan chewing are under the common initiative of tobacco cessation programs. The major initiatives are mass media campaigns, community programs and tobacco cessation clinics(151). Similar to any other psychoactive substance, motivating individuals addicted to paan chewing to refrain from the habit is challenging. A recent study on the effectiveness of a national mass media campaign against smokeless tobacco reported that the campaign achieved its goal of increasing general awareness(152). But the translation of this awareness into cessation of the habit has yet to be investigated. However, mass media communications may increase judgement of societal risk without affecting the estimation of personal risk(153). In other words, although the general awareness about the risk associated with the habit increases, the awareness of one's own risk does not increase. Results from a survey conducted among a high-risk population in Kerala supports this finding; 75% of paan chewers were aware that the habit could lead to oral cancer, yet they continued to chew(154). One-on-one tobacco cessation counselling could also have the same disadvantage; a recent study reported that in India, a very low

proportion of tobacco users (10%) who attempted to quit utilised any cessation aids. Moreover, the use of cessation aids were negatively associated with success in attempting to quit tobacco(155). These findings point towards the need for an individualised risk assessment and targeted counselling. For the development of such individualised risk assessment protocols, a better understanding of how the risk changes according to the dose of different dimensions of paan chewing is essential.

The habit of paan chewing may be different in each individual in terms of the quantity, frequency and duration of use of paan and a complex interplay among these dimensions may determine their risk profile. Hence, understanding the dose-dependent variation in risk of oral cancer among individuals with the habit of paan chewing is an essential stepping stone in understanding the biological processes and pathways which leads to differential incidence of oral cancer seen among exposed individuals. It is of particular importance to study the Indian population due to the high proportion of individuals with this habit. In addition, the habit of paan chewing has been known in this part of the world for more than 2000 years(1) and due to centuries of exposure through several generations, genetic susceptibility or resistance may have developed, which could also contribute to the differential risk among exposed subjects. Therefore, it is important to study this risk profile in this population.

Most of the previous studies adopt a linear trend analysis when examining the dose-response relationship between paan chewing and oral cancer risk. Studies have shown that pure linearity is rare in natural situations and that the widely followed linear trend analyses are flawed in their assumptions(156). Our study (manuscript II) contributes to the knowledge on the dose-response relationship between paan chewing and oral cancer using a flexible modeling technique of restricted cubic spline regression. The technique has shown to be superior to linear trend analysis as it does not impose a linearity assumption(156).

In summary, this thesis investigates whether parental paan chewing habit is associated with their children´s habit and how the risk of oral cancer changes

according to the dose of the habit. Thus, it contributes to the knowledge of paan chewing in a hospital based sample from Kerala.

4. STUDY OBJECTIVES

The general aim of the project is to generate knowledge regarding the continuity of paan chewing between generations in South Indian families. In addition, we assess the dose-response relationship between paan chewing and oral cancer. The specific objectives are as follows:

- To evaluate the association between parental paan chewing and participant's paan chewing among a subset of the South Indian population (Manuscript I).

- To estimate the maternal and paternal contribution to the intergenerational psychosocial transmission of paan chewing among a subset of the South Indian population (Manuscript I).

- To evaluate whether participants' perception of their relationship with their parents is associated with participant's paan chewing (Manuscript I).

- To estimate the dose-response relationship between lifetime cumulative exposure to paan chewing and risk of oral cancer among a subset of the South Indian population (Manuscript II).

- To investigate the association between years since cessation of paan chewing and risk of oral cancer among a subset of the South Indian population (Manuscript II).

5. METHODS

5.1 Study design

Case-control studies are observational studies where the participants are selected based on the presence of a particular event of interest, and exposure is measured and compared between these two groups. This study design is known to be efficient for studying the aetiology of rare diseases such as cancer. Information on exposures of interest is collected in a retrospective fashion, either through interviews or by consulting medical records. Cases are those participants in whom the event of interest has occurred and controls are those in whom it has not.

The HeNCe Life study is a multicenter hospital based case-control study investigating the aetiology of upper aerodigestive tract cancers. The study is being conducted in three different countries: India, Canada and Brazil. The research questions of this thesis are investigated with data drawn from the Indian chapter of this study.

5.2 Study site

The HeNCe Life study - India was conducted from 2008 to 2012 at Government Dental and Medical Colleges, Kozhikode, South-India. The city of Kozhikode is located in a Southern province of India called Kerala. Situated in the Northern part of Kerala, these institutions serve as the tertiary centers for referrals from all other regional health centers. Both of these institutions are located on the same campus and have the same catchment area. The specialities of both institutions do not overlap, hence they could essentially be considered as one large institution.

5.3 Eligibility criteria

The common eligibility criteria to enter the study for cases and controls were as follows: the participant should: (i) be born in India; (ii) be at least 18years of age; (iii) reside within 150km of the study site; (iv) have no previous history of cancer or HIV infection; (v) have no cognitive or mental disorder; and (vi) speak either English or the local language, Malayalam. Patients who were unable to respond due to the severity of their disease or not willing to give informed consent were not eligible. The geographical restriction of 150 km was established to ensure that cases and controls come from the same source population or study base(157).

5.4 Case and control definition

Cases were incident oral squamous cell carcinoma (OSCC) patients, who reported consecutively at the Department of Oral Pathology and Microbiology of the Government Dental College, and the cancer outpatient clinic of the Government Medical College. Case ascertainment was done through histopathological examination, which is considered the diagnostic gold standard for oral cancers. Squamous cell carcinomas at stages I to IV manifested on the tongue, gingiva, floor of mouth, palate, retromolar area and vestibule of mouth, cheek mucosa, and tonsil were included (ICD-10 codes C00.3 – C06.9, C09). Malignant neoplasm of the external lip (C00.0-C00.2), major salivary glands (C07, C08) and nasopharynx (C11) were excluded due to their different histology and aetiology. If eligible, cases were recruited immediately after the histopathological diagnosis. Patients who were currently undergoing treatment for cancer were not eligible as their treatment could interfere with the biomarkers under study. To avoid survivor bias, temporal ambiguity between exposure and disease, and reverse causality, prevalent cases of oral cancer were not eligible(158,159).

Control participants were cancer free patients consulting at eight different outpatient clinics (dentistry, ophthalmology, gynaecology, gastroenterology, ENT, nephrology, dermatology and orthopaedics clinics) of the above mentioned institutions. They were frequency matched to cases according to age (periods of five years) and sex.

To ensure that no particular disease group was overrepresented, no single department contributed more than 20% of the total controls. In addition, to avoid over-representation of exposures relevant to oral cancer among controls and to reduce Berkson's bias, they were recruited from a strictly defined list of non-chronic diseases unrelated to tobacco or alcohol habits(157).

5.5 Ethical approval and informed consent

The study protocol was reviewed and approved by the ethics committees of both Indian institutions, as well as McGill University. Eligible patients were approached by a research assistant and the study protocol was explained to them in the local language (Malayalam) or in English, and the informed consent form was given to them to read and ask questions, if they had any. Willing participants were asked to sign the informed consent form (English or Malayalam) (Appendix I). One copy was given to them and the other was filed in a locked cabinet at the study site. The consenting procedure was carried out in the presence of a witness who also signed the form.

Route sheets were also filled for every participant with personal information (name, address and contact information) and used to schedule the interview. These route sheets were kept securely in locked cabinets at the study site.

5.6 Data collection

5.6.1 Recruitment procedure

Three qualified dentists, including the author, were appointed as research assistants (RA) and were responsible for participant recruitment and data collection. They were trained in data collection and study procedures by the principal investigator (PI). An interviewer's guide and a DVD featuring step by step study procedures were provided at the site for reference. The study was coordinated by an international coordinator who was responsible for providing the RA with a matching list of control subjects to be recruited each month. This list included the particular age groups, sex and department from which the control subjects needed to be recruited that particular month. The eligibility of oral cancer

patients seen at the clinics was assessed by the RA every day and eligible patients were invited to participate in the study immediately after their diagnosis.

Control patients were recruited based on each month's requirement indicated in the matching list. Different departments had different days of the week assigned as outpatient clinic days, RA visits to the control clinics were based on this schedule. During each visit, the clinic's outpatient appointment list was scanned for eligible participants and they were randomly approached with invitation to participate in the study. This procedure was repeated until the required number of participants was recruited from each clinic.

5.6.2 Participation rate

During the period of September 2008 to April 2012, 409 eligible oral cancer patients were identified, out of which 350 participated in the study, resulting in a participation rate of 85.6% among cases. However, the participation rate was low among controls: out of 837 eligible patients, only 371 participated, resulting in a 44.3% participation rate. Plausible reasons for the low participation rate among controls and its implication for the study results are addressed in the discussion section.

Individuals who were not willing to take part in the study were asked to provide the reason for non-participation; however, they were free to refuse. In addition, demographics (age and sex) of the non-participating individuals were collected from the appointment list. Non-participating cases had a significantly higher mean age compared to participating cases (mean age ± SD = 68.36 ± 16.0 and 60.77 ± 11.2 years for non-participating and participating cases, respectively, $p < 0.001$). This result is in agreement with the most common reasons given for non-participation among oral cancer cases: weak general health and advanced disease stage. However, no such difference in mean age was found among controls (Table 5-1). Almost half of participating cases were females (154 (44.0%)) and no significant sex difference was found between participating and non-participating cases and controls (Table 5-1).

Table 5-1: Distribution of participating and non-participating cases and controls

	Participating cases	Non-participating cases	P value
Mean age ± SD	60.77 ± 11.3	68.36 ± 16.0	<0.001
Sex (n (%))			
Females	154 (44.0)	32 (54.2)	
Males	196 (56.0)	27 (45.8)	0.144
	Participating controls	Non-participating controls	P value
Mean age ± SD	60.53 ± 11.7	61.43 ± 11.1	0.256
Sex (n (%))			
Females	168 (45.3)	193 (41.4)	
Males	203 (54.7)	273 (58.6)	0.262

5.6.3 Study instruments

5.6.3.1 Questionnaire

The informed consent procedure was followed by a face-to-face interview with the participant, which lasted approximately 1 ½ to 2 hours. A questionnaire and a life grid technique were used for this purpose. The questionnaire was developed based on questions used for different studies: British Birth Cohort (BBC) - 1946, BBC 1958, British Civil Servants: Whitehall Study II, and IARC studies on upper aerodigestive tract cancers(160–162). Based on a focus group discussion the questionnaires were adapted to Indian context and were translated into the local language (Malayalam) and tested in a pilot study conducted at the same site. The final questionnaire was back-translated into English (Appendix – II) and was cross-checked for errors.

The questionnaire collected information on demographics, medical history, indicators of socio-economic position (e.g., education, occupation, housing conditions and other material amenities), participants' and their parents' behavioural factors (e.g., smoking, paan chewing, alcohol consumption), childhood and adulthood dietary habits (e.g., diet patterns and consumption of spices), general health and build, oral hygiene and oral health (e.g., decayed, missing and filled teeth), family history of cancer, marital life and social support.

5.6.3.2 Life grid

Means et al showed that providing participants with a temporal reference system such as a personal time line improves recall(163). Based on this finding and other methods known to improve recall, Blane developed a life grid to be used in retrospective data collection(164).

We adopted a modified version of this life grid to improve the quality of data collected. The life grid consists of a virtual time line on a sheet of paper. A central vertical line denotes the interviewee's age in years on which horizontal reference lines are placed at 5-year intervals. The grid is divided into four columns: housing, education or job, habits and others. The housing section is used to record the age or dates when the participant changed houses and other major changes related to residential status. Ages at start and end of jobs, habits such as smoking, alcohol or paan chewing, and education are recorded in corresponding sections. Finally, another section is used to record dates of any major life events such as marriage, birth of first child, or historical events like wars, strikes or sporting events occurred during the participant's lifetime. The life grid is introduced to the participant at the beginning of the interview. Once the major life events are noted referring to the central age line, information regarding other sections is collected by cross-referring them with these events. If there are any overlapping or unclear dates or periods, they are discussed and clarified with the participant with the help of the life grid.

The use of life grid in retrospective data collection has been shown to improve the accuracy of recall(165); moreover, it helps the RA to establish a good rapport with the participant, which is essential for long interviews such as ours(166).

5.7 Quality assurance and data management

All the study procedures were conducted strictly following the protocol as described in the interviewer's guide. Log files for participating and non-participating subjects were maintained at the site and sent to the international PI monthly. On the basis of these log files, the cases and controls frequency matching lists were prepared by the study coordinator in Canada and sent to the

Indian site. To assess the reliability of data collection, close to 10% of participants were randomly selected and re-interviewed after 6 to 12 months. During this re-interview session, the RA or participant was not allowed to consult any previous interview records. The RAs' work was strictly monitored by site collaborators who were in regular correspondence with the international PI.

Data were entered into an online database using the FileMaker version 11 software for Windows(167). The secure online database server was maintained by the international study coordinator in Canada. After completion of data entry, multiple data cleaning cycles were conducted with the help of the study coordinator and any data entry errors were resolved. Log files were also maintained for these data cleaning cycles.

5.8 Working definition of paan

Although there are three basic ingredients in paan (betel leaf, areca nut, slaked lime), most often tobacco is added to the mixture. Betel quid with tobacco is the most prevalent form of paan in Kerala, where the study was conducted(23). Since participants can use different ingredients in different quantities and the same person can use different ingredients at different time points in life, it is hard to standardise exposure definitions. Hence, a working definition of paan was adopted in our study: any combination containing areca nut, tobacco, or both.

5.9 Definition of variables and measures

The following section discusses how exposures were measured and variables of interest were computed.

5.9.1 Participant's behavioural habits

5.9.1.1The habit of paan chewing

Participants who had the habit of paan chewing for at least one year at any point in their life were considered as 'ever chewers' of paan. Ever chewers who had stopped the habit for at least one year from the date of interview were considered as "past chewers".

Participants who had never chewed paan in their lifetime were considered as "never chewers". Moreover, changes in paan chewing history which were less than one year in duration were not taken into consideration.

A quid is defined as a substance or mixture of substances which is chewed and retained in the mouth, and sometimes swallowed. Frequency of paan chewing was defined as number of quids of paan chewed per day. One may use paan in different frequencies at different points of life. We collected a detailed and comprehensive habit history from ever chewers, recorded in periods based on type of paan and frequency of use (Appendix II page 161). For example, if a man started chewing paan at 20 years of age and used 2 different types, each in 3 different frequencies (quids/day) until the age of 60 years, his habit history would consist of 6 periods. For each period, the following information was collected: (a) age at the start of a particular frequency (start age); (b) age at the change or end of that frequency (stop age); (c) frequency of use (quids per day/month/year); (d) minutes of use each time they chewed paan; and (e) type of paan. Different dimensions of paan chewing were computed from this information, as detailed below.

Lifetime duration of paan chewing (in years)

If *'i'* denotes the number of same frequency periods in a participant's paan chewing habit history, the duration of the i^{th} period is computed as

$$\boldsymbol{Duration_i = ((Stop\ age_i - Start\ age_i) + 1)}$$

and

$$\boldsymbol{Life\ time\ duration = \sum_{1}^{i} Duration_i}$$

In other words, the duration of each period was computed as (Stop age – Start age) +1. The integer 1 was added to the equation to make it inclusive of both start age and stop age. The lifetime duration was computed as the summation of individual durations.

However, if a participant used two different types of paan during the same time period, the duration of that period was only counted once while computing life time duration variable.

Average frequency of paan chewing (in quids/day)

If *'i'* denotes the number of same frequency periods during a participant's paan chewing habit history, and frequency of the i^{th} period is denoted as '$frequency_i$'; then the average frequency of PCH was computed as

$$Average\ frequency = \frac{\sum_1^i (frequency_i * duration_i)}{life\ time\ duration}$$

In other words, the average frequency of paan chewing was computed as a weighted average of frequencies of different periods, where each frequency is weighted according to its duration. The average frequency was computed using a unit of quids/day.

Cumulative chew years of paan (chew years)

An indicator of the cumulative exposure to paan was created, analogous to the cigarette years variable commonly used for cigarette smoking. The equivalent of pack years could not be estimated, since paan is not sold in packs. One chew year is equivalent to chewing one quid of paan every day for one year, and is computed as follows:

$$Chew\ years = \sum_1^i Duration_i * frequency_i$$

where 'i' is the number of same frequency periods of a participants' paan chewing habit history. This measure was considered as the exposure of interest to assess dose-response relationship between the habit of paan chewing and oral cancer (manuscript II).

Never chewers of paan were given a zero value for all the above mentioned measures of paan chewing.

Years since quitting (quit years)

For past chewers of paan, the years since quitting was computed by subtracting the age at which the participant stopped paan chewing from the age at which the interview was conducted. This measure was zero for current and never chewers of paan and it was the exposure of interest to investigate the effect of quitting paan on risk of oral cancer (manuscript II).

Types of paan

As noted in the literature review, the ingredients of paan can change according to geographical area or personal preferences. We collected comprehensive data on the type of paan chewed through eight different combinations: (1) only tobacco; (2) betel quid (areca nut, betel leaf and slaked lime) with tobacco; (3) only betel quid; (4) areca nut with tobacco; (5) only areca nut; (6) pan masala (commercially available paan); (7) only betel leaf; (8) any other combination. As per our working definition of paan, any combination which included areca nut, tobacco or both was considered as paan (all the above combinations except number 7).

5.9.1.2 Tobacco smoking

Information was collected on two different forms of tobacco smoking: cigarette and bidi smoking. Participants were considered as ever smokers if they smoked tobacco for at least one year in their lifetime. Similar to paan chewing tobacco smoking history was also collected in periods of same frequency and type. In addition, commercial brand and type (with or without filter) of cigarette were also collected. Cumulative exposure variables for tobacco smoking were computed as pack years, where one pack year of cigarette is equivalent to smoking one pack of cigarettes every day for one year. According to Indian standards, one pack of cigarette contains 10 cigarettes and one pack of bidi contains 20 units. Hence, computations of pack years were done accordingly. For example, a man who smokes 5 cigarettes and 15 bidis per day from 30 to 50 years of age will acquire 10 pack years of cigarette and 15 pack years of bidi, respectively.

Lifetime pack years of cigarettes and bidi, used as continuous variables, were considered as confounders in the association between paternal paan chewing and participants paan chewing manuscript I), and in the association between paan chewing and oral cancer (manuscript II).

5.9.1.3 Alcohol consumption

Similar to smoking and paan chewing, participants were considered "ever drinkers" if they had the habit for at least one year. Information on alcohol consumption was collected based on the type of beverage. Five different types of beverages were considered: (i) toddy – wine from the coconut tree; (ii) wine; (iii) beer; (iv) hard liquor (arrack, whisky, vodka, brandy, gin, rum, grappa); and (v) any other type of alcohol. Five different units of consumption were considered for each type: (i) small glass - 50ml; (ii) medium glass – 100ml; (iii) large glass-250ml; (iv) half bottle - 330ml; and (v) full bottle – 750ml.

Different types of beverages were first standardized based on their percentage of alcohol content as follows: toddy and wine – 10 %, beer - 5% and hard liquor – 50%(168). The lifetime consumption of ethanol in millilitres was computed by first multiplying the duration of each type to the corresponding frequency of use and later summing up this measure for all types.

To make this measure comparable to a consumption of standard drinks in North America (18 ml of alcohol)(169), the lifetime consumption was divided by 18, resulting in the measure - number of standard drinks consumed during the lifetime. Average lifetime intensity, the number of standard drinks per week, was computed as follows:

$$Standard\ drinks\ per\ week = \frac{Number\ of\ standard\ drinks\ consumed\ in\ lifetime}{Total\ years\ of\ habit * 52\ weeks}$$

This measure (standard drinks per week) was considered as a continuous variable in the analysis (manuscript II).

5.9.2 Parental behavioural habits

Participants were asked about their parents' smoking, paan chewing and alcohol consumption. Maternal and paternal habits were measured separately, and were recorded as categorical variables. Parental paan chewing and smoking habit were dichotomized as ever or never users. Parental alcohol consumption was categorized based on the frequency of consumption: (i) never; (ii) occasionally; (iii) weekly once/ during weekends; (iv) 3-4 times per week; and (v) daily.

5.9.3 Perceived parenting behaviour

Participants were asked about the man and the woman who cared for them the most during their childhood (0-16 yrs). This question was followed by others on participants' perception of the parenting behaviour of the person who cared for them the most. The perceived parenting questionnaire used to measure this perception was adapted from the Whitehall II study(170), and is composed of seven items for each caretaker. Participants responded to questions pertaining to different dimensions of parenting using a four-point scale (not at all, a little, quite a lot, and a great deal) (Appendix II). The latent constructs of these variables were identified through an exploratory factor analysis(171,172). Later, to help in interpretation, the questions which were loading onto the same latent variable were combined by adding their scores to create an index. In total, two latent constructs were identified for each parent, resulting in four variables which were labelled maternal warmth, maternal strictness, paternal warmth and paternal strictness. An in-depth discussion of this analysis is provided in the additional analysis section of manuscript I.

5.9.4 Lifetime material deprivation indicator

Material deprivation is considered as an indicator of individuals' SEP. A lifetime index of material deprivation was created through a series of computations of three different groups of variables - housing tenure (e.g., rented or owned house), housing condition (e.g., material used to build floor, roof and wall, number of

bedrooms, number of persons living together) and amenities (e.g., television, radio, refrigerator).

Information on these variables was collected in three different life stages, childhood (0-16 years), adolescence (17-30 years) and adulthood (after 30 years), based on the house in which the participant lived the longest for each stage. Different number of variables contributed to this information at each life stages: childhood (9), adolescence (11) and adulthood (14). Further, based on the presence or absence and cost of the material, each of these variables were dichotomized into high material deprivation with a value of 0 (low SEP), and low material deprivation with a value of 1 (high SEP). Following this step, a material deprivation index was created by adding these binary variables for each life stage. Hence, a continuous variable was created with scores ranging from 0 to 9 in childhood, 0 to 11 in adolescence, and 0 to 14 in adulthood.

For easier interpretability, material deprivation indices for each stage were further categorized as low and high based on the median score among control participants. These variables were used as binary indicators of material deprivation for each life stage.

A participant can be at different levels of the material deprivation at different stages of life, so we created a cumulative variable based on the number of life stages spent at a particular level of material deprivation. Hence, the final variable for lifetime material deprivation included four categories: (i) all three life stages spent in high material deprivation (ii) two stages of high and one stage of low material deprivation; (iii) two stages of low and one stage of high material deprivation; and (iv) all three life stages spent in low material deprivation. This variable was considered as an indicator of lifetime SEP and was used as a confounder in the association between paan chewing and oral cancer (manuscript II). In addition, childhood material deprivation was used as proxy measure of parents' SEP in the association between parental paan chewing and participant's paan chewing (manuscript I).

5.9.5 Participants' education

Different dimensions of participants' education were measured: any formal education or not, literate or not (able to read and write at least the local language), years of formal education, highest level of education attained (categorical) and whether the participant had ever failed a school year. Moreover, if the participant never had any formal education, the reason for that was also collected.

The same education level can have a different meaning at different periods in history, hence the education level of participants belonging to different birth cohorts should be considered within its historical context. Kerala, where the study was conducted, saw some significant changes in its education system around 1950(173). In light of these two considerations, we computed the education level of participants as follows. For participants who were born before or in 1950, more than four years of formal education was considered as a high education attainment, whereas for participants born after 1950 the same category was attributed to those with more than eight years of formal education.

5.9.6 Parents' education

Participants were asked about their parents' education attainment, whether or not their parents had any formal education and if they had any, how many years of education they had completed. Based on this information, maternal and paternal education was categorised as a binary variable: (0) uneducated and (1) educated (at least one year of formal education). This variable was considered as a potential confounder in the association between parental paan chewing and participant's paan chewing (manuscript I).

5.9.7 Dietary factors

Among dietary factors, the weekly frequencies of fruit and vegetable consumption were measured. Since the participants recruited at hospital clinics may have changed their diet preferences or patterns due to their diseases, we collected information on dietary factors in adulthood until two years prior to the diagnosis.

Information was collected on the frequency of consumption of fruits such as bananas, citrus fruits (oranges, lemons, grapefruits), apples/pears, and local tropical fruits such as mangos, jackfruits, pineapples and papayas. Information was also collected on vegetables such as cruciferous vegetables (cabbages, cauliflowers) yellow vegetables (tomatoes, carrots, pumpkins), spinach, and any other type of vegetables consumed. A continuous summary variable was computed by adding the frequencies of fruits and vegetables separately, denoting the weekly consumption of any type of fruits and vegetables, respectively. The frequency of vegetable consumption, as a continuous measure, was considered as a potential confounder in the association between paan chewing and oral cancer (manuscript II).

5.9.8 Oral health factors

An oral health assessment was carried out by professionally trained dentists in a dental clinical setting with the help of a mouth mirror and standard source of light. The decayed/missing/filled teeth (DMFT) index was computed for each participant. Healthy teeth were coded as 0, decayed teeth as 1, filled teeth as 2 and missing teeth as 3. The counts of each of these characteristics were considered as continuous variables, out of which the number of missing teeth was considered as a potential confounder in the association between paan chewing and oral cancer(manuscript II) based on *a priori* knowledge(74–76).

5.9.9 Religious belief

The paan chewing habit is an integral part of Hindu culture, to the extent that it is offered as a token of respect to guests in family functions and religious events(5). Moreover, studies have shown that religious beliefs are strong predictors of the prevalence of paan chewing(174). Information on participant's religion, age when they started following the religion, and caste or tribe they belonged to (if any) were collected. Since most subjects belonged to the Hindu religion and due to the importance of paan chewing in Hindu culture, a binary variable (Hindu / Non-Hindu) was considered as a potential confounder in the association between parental paan chewing and participant's paan chewing (manuscript I).

5.10 Missing data

In following section, handling of missing data is discussed for variables pertaining to each manuscript separately. Particular information was considered as missing if the subject was unable to recall the information even after using the life grid technique or if the interview was conducted with the use of a proxy who did not have the information.

5.10.1 Management of missing values (manuscript I)

The association between parental paan chewing and participant's paan chewing (manuscript I) was investigated among control subjects. A sufficient period is necessary for the intergenerational transmission of paan chewing to occur, thus this research question is based on the underlying assumption that participants were raised by their parents during childhood through adolescence. Hence, participants who reported that they were not raised by their parents (n=52, 14%) were excluded. Furthermore, one subject had missing data for paternal paan chewing, one of our exposures of interest, thus this participant was also excluded, resulting in a total sample size of 318. Out of these 318 subjects, 51 (16%) participants had missing information, which was concentrated on two variables: paternal education (48, 15.1%) and maternal education (42, 13.2%). Moreover, out of the 51 participants who had missing values, 39 (76.5%) participants had missing values for both paternal and maternal education. Since the percentage of missing information was not negligible, missing values were imputed through multiple imputation.

5.10.1.1 Multiple imputation by chained equation modeling (MICE)

Multiple imputation (MI)(175) is a statistical technique to handle missing data, which has been shown to be robust and powerful compared to several other methods(176). The basic concept of MI is to estimate the plausible values of missing data from the observed data with a random component incorporated in the estimation process.

Multiple datasets are created with different values for the missing data, and analyses are done separately for each dataset to get a set of parameter estimates which are then pooled based on certain rules. Multiple imputation is usually done when data are missing at random (MAR) – that is, the probability that data is missing does not depend on the value of the missing data itself, but can depend on the observed data of other variables. We assumed that this applies to our study since there is no statistical method to test whether the missing data is MAR, and there is no logical reason to assume otherwise.

We adopted multiple imputation by chained equation (MICE) to impute the missing values in paternal and maternal education variables. MICE is a method of multiple imputation that is robust enough to handle categorical as well as continuous variables(177). MICE is a model based approach where the missing values are estimated through simulated draws from a posterior predictive distribution which is derived from regressing the variable with missing values on all other variables in the data(178).

Patrick Royston's STATA command for MICE (`ice`)(179) was used for imputation with the variables in the model that could possibly predict the missing value: parent's SEP, participant's education, participant's and parent's behavioural factors (smoking, alcohol, paan chewing), religion, age, sex, perceived parenting factors (parental warmth and strictness), interviewer and proxy. Twenty imputed datasets were created, and analyses were carried out using Carlin et al's STATA command (`mim`) which pools the parameter estimates from the multiple datasets and computes confidence intervals according to Rubin's rules(180).

5.10.2 Management of missing values (manuscript II)

The dose-response relationship between paan chewing and risk of oral cancer was investigated with the full dataset including 350 oral cancer cases and 371 non-cancer controls. Since parental education is not considered as a potential confounder in this analysis, missing values for these variables are not considered. However, 35 (4.9%) participants had missing information for the life course SEP

variable, and they were almost equally distributed among cases (16, 4.31%) and controls (19, 5.43%). Imputation of missing values is usually pursued if the percentage of missing data is greater than 5%; otherwise complete-case analysis is carried out after listwise deletion of missing data. This is based on the assumption that if only a small portion of data is missing, the remaining complete data represents a simple random sample of the target data, and hence the results would not be biased(181). Since the percentage of missing value in our dataset is small hence negligible, listwise deletion of missing values for the life course SEP variable was performed, resulting in a dataset with a sample size of 686 (331 cases and 355 controls) participants. This is the basic dataset used for analyses in manuscript II.

5.11 Overview of statistical analysis

The following section contains an overview of the statistical analyses conducted in the two manuscripts. All analyses were performed with STATA-12 for Windows(182). In addition to the use of descriptive statistics to explore the data and test crude associations, statistical models were pursued in the manuscripts as described below.

5.11.1 Binary logistic regression

Binary logistic regression was used to model the association between participants' paan chewing and their parents' habit (manuscript I). Binary logistic regression is a type of generalized linear model used to predict binary dependent variables.

The logistic regression equation can be written as

$$\ln\left(\frac{p}{1-p}\right) = \beta_0 + \sum_{i=1}^{k} \beta_i * X_i$$

Where

p is the probability of Y =1, or the probability that the outcome will occur;

X_i is the i^{th} predictor variable, i = 1, 2, 3....k;

β_0 is the log odds of probability of outcome when all predictor variables (X_i) have a value of zero;

β_i is the regression parameter associated with the i^{th} predictor variable such that the odds ratio associated with a one unit increase in the i^{th} predictor variable X, when all other covariates are kept constant, is

$$OR_i = e^{\beta_i}$$

In our study, participant's paan chewing (never or ever chewer) was the dependent variable, and mother's and father's paan chewing were the main exposures of interest. The next section discusses how potential confounders were selected for this analysis.

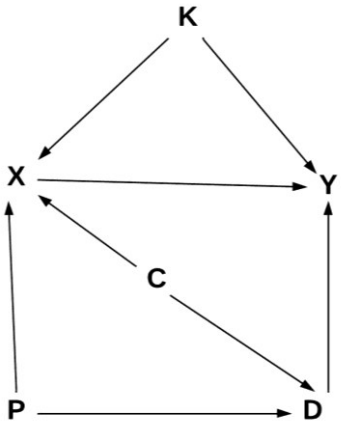
5.11.1.2 Model selection using directed acyclic graphs

Model selection was based on *a priori* knowledge and directed acyclic graphs (DAGs). DAGs are a type of causal diagram introduced by Pearl in 1995(183). They are visual representations of the causal relationships between variables in a source population. DAGs based on *a priori* knowledge are widely used to help plan data collection and analysis, communicate results, and avoid pitfalls when selecting confounders(184,185).

A hypothetical DAG (Figure 5-1) is used to briefly explain the concepts. An arrow headed line from variable X to Y denotes that X is a direct cause of Y, and Y is a resultant of X. A variable P is called an indirect cause of Y if there is a series of arrow headed lines (a path) from P to Y which goes through other

variables (D). Any path which leaves X through an arrow head entering it and ends in Y is called a backdoor path from X to Y.

Figure 5-1: Hypothetical directed acyclic graph



Here, there are three backdoor paths from X to Y: X-K-Y, X-C-D-Y, X-P-D-Y. A path is considered as blocked when a variable in the path is controlled or adjusted. For complete controlling of confounding to occur, all backdoor paths from X to Y should be blocked by adjusting for one or more variables in the path. A minimum set of such variables, so that no remaining unblocked backdoor path exists, is preferable to adjusting for all the potential confounders. In the above DAG (Figure 5-1), the minimum set of confounders is {K, D}; by adjusting for these two variables, all the backdoor paths from X to Y are blocked except the direct path (X-Y), which is the association of interest.

We used DAGs to identify the minimum set of confounders to be taken into account to estimate the true association between parental and participant's paan chewing (manuscript I -Figure 6-1 & 6-2). Age, religious beliefs, parent's SEP, participant's smoking and alcohol consumption, and perceived parenting behaviours were identified as the minimum set of potential confounders to be included in the multivariate analyses. Further, to separate the effect of maternal and paternal PCH, they were mutually adjusted for one another in the corresponding models. Odds ratios and 95 % confidence intervals estimated from logistic regression models were reported.

5.11.2 Restricted cubic spline regression

Restricted cubic spline regression was used to model the dose-response relationship between PCH and oral cancer (manuscript II).

Since the cumulative chew year is a comprehensive summary variable for lifetime exposure to paan, it was selected to investigate the dose-response curve. Moreover, Leffondre et al showed with the example of smoking history and lung cancer that when modeling different dimensions of exposure, it is preferable to use a summary variable(186). They also showed the significance of centering the continuous exposure variables and including an indicator variable to take into account the qualitative difference between participants with and without the habit(186). Since these considerations are also applicable to paan chewing, we centered the cumulative chew year variable (chew years) and years since quitting paan (quit years) for ever chewers of paan while keeping zero for never chewers. Centering is a linear transformation of a continuous variable where the centered variable is computed by subtracting the mean from each observation. This transformation does not change the estimated effect(187), but allows the parameter of the indicator variable to have a meaningful interpretation. An indicator variable with three categories (never chewer, current chewer and past chewer), with never chewers as the reference category, was included in the model. The addition of this indicator variable is essential to differentiate values of quit years between current chewers and never chewers, since both have a value of zero quit years.

The model for dose-response could be written as

$$\ln\left(\frac{p}{1-p}\right) = \beta_0 + \delta_i S_i(Chew\ years) + \beta_2 * quit\ years + \beta_3 * current\ chewer + \beta_4 * past\ chewer + \sum_{t=0}^{n} \theta_t * X_t$$

Where,

p is the probability of being an oral cancer case;

β_0 is the logodds of the probability of the outcome when all predictor variables have a value of zero;

β_2 is the logodds of the effect of a one unit increase in years since quitting among past chewers;

β_3 is the log odds of the effect of being a current chewer with mean amount of chew years compared to a non-chewer;

β_4 is the log odds of the effect of being a past chewer with mean amount of chew years and quit years compared to a non-chewer

X_t is the t^{th} covariate in the model, t = 1, 2, 3 ...n

θ_t is the log odds of the effect of X_t;

S_i (Chew years) is the restricted cubic spline function of chew years

A restricted cubic spline function will have K-2 parameters, where K is the number of knots. We tested five different models with an increasing number of knots (3, 4, 5, 6 and 7).

The position of knots was chosen from percentiles of chew years among ever chewers using a modified version of Harrell et al's recommendation of placing knots at equally spaced percentiles(188). The knots' positions were as follows

3 knots – 5th, 50th, 95th percentiles;

4knots – 5th, 35th, 65th, 95th percentiles;

5knots – 5th, 27.5th, 50th, 72.5th, 95th percentiles;

6knots – 5th, 23rd, 41st, 59th, 77th, 95th percentiles;

7knots – 5th, 20th, 35th, 50th, 65th, 80th, 95th percentiles

The best-fit model was considered to be the model with the lowest AIC value. A likelihood ratio test was performed between the linear model and the best-fit model to check whether the best-fit model was anything other than the linear model. The dose-response curve was interpolated using the spline parameters from the best-fit model. We used the user written command `mkspline2` to compute spline functions of chew years and `xbrcspline` to estimate differences in the predicted responses (linear combinations of coefficients) and the corresponding 95% confidence intervals after restricted cubic spline regression, which were then plotted against the values of chew years. Since estimated spline parameters cannot be interpreted independently, the shape of the dose-response curve is used to interpret the relationship. Model selection was based on *a priori* knowledge; potential confounders considered were age, sex, smoking (cigarette pack years and bidi pack years), alcohol (drinks per week), life course socio-economic position, number of missing teeth, vegetable consumption.

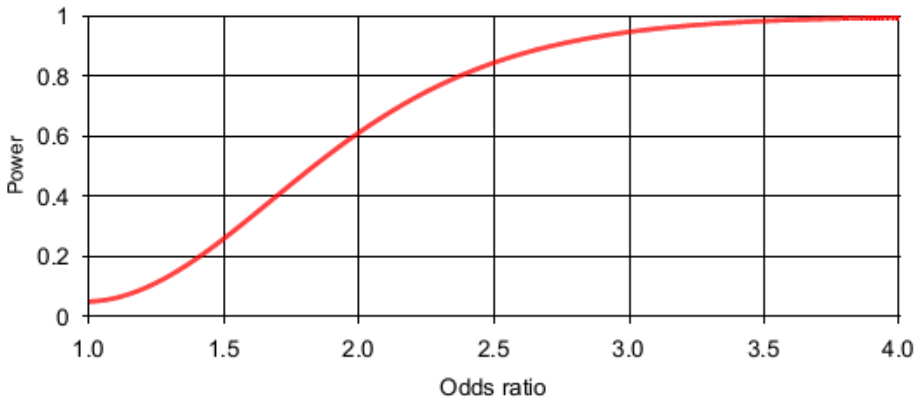
5.12 Sample size and power considerations

This section contains the post-hoc power analysis for each particular analysis in manuscripts I and II. Power analysis were done using PS software 3.0.43 for Windows(189).

5.12.1 Association between paternal and participant's paan chewing

The data for this analysis included 318 observations (52 ever paan chewers and 266 never chewers). Figure 5-2 shows the attained power for a range of odds ratios and for a prevalence of paternal chewing among non-chewing participants of 0.29 (P0). The significance level (probability of Type 1 error) was set at 5%. With the restricted sample size, the study has the desired power of 80% to detect an odds ratio of 2.37 or more if the true odds ratio of paternal paan chewing among ever chewers of paan is 3.05 compared to never chewers, the study had a power of 95.3% to reject the null hypothesis.

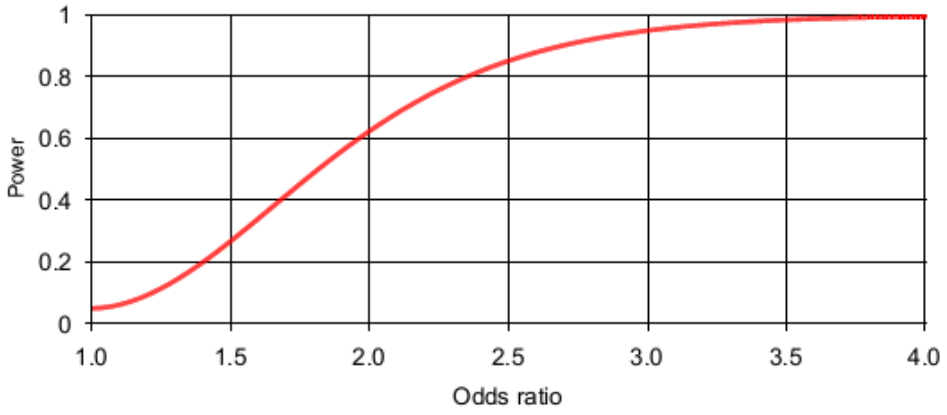
Figure 5-2: Post hoc power analysis for the association between paternal and participant's paan chewing (sample size=318, α=0.05 and P0 = 0.29).



5.12.2 Association between maternal and participant's paan chewing

The association between maternal and participant's paan chewing was investigated using logistic regression in the same dataset as above. Figure 5-3 shows the attained power for a range of odds ratios and for a prevalence of maternal chewing among non-chewing participants of 0.42 (P0). The study has the desired power of 80% to detect an odds ratio of 2.35 or more. If the true odds ratio of maternal paan chewing among ever chewers of paan is 2.40 compared to never chewers, the study had a power of 81.9% to reject the null hypothesis.

Figure 5-3: Post hoc power analysis for the association between maternal and participant's paan chewing (sample size=318, α=0.05 and P0 = 0.42).

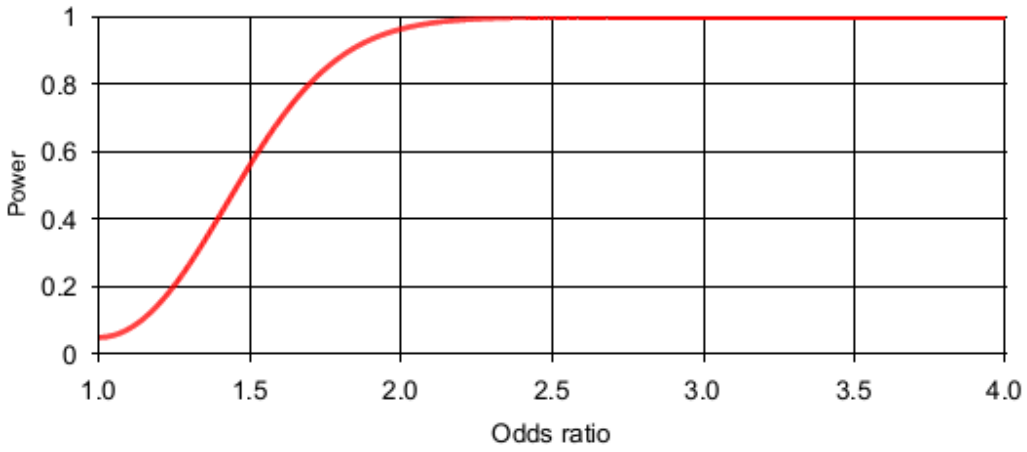


5.12.3 Association between paan chewing and oral cancer

The association between paan chewing and oral cancer was performed as a preliminary analysis before investigating dose response relationship. The dataset for this analysis included 686 observations (331 cases and 355 controls).

Figure 5-4 shows the attained power for a range of odds ratios and for a prevalence of paan chewing among control participants of 0.17 (P0). The study has the desired power of 80% to detect an odds ratio of 1.70 or more. If the true odds ratio of paan chewing among is 13.21 compared to never chewers, the study had a power of more than 99% to reject the null hypothesis.

Figure 5-4: Post hoc power analysis for the association between paan chewing and oral cancer (sample size=686, α=0.05 and P0 = 0.17).



6. MANUSCRIPT - I

Maternal and paternal contribution to intergenerational psychosocial transmission of paan chewing habit in South India

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Abstract:

Background: Paan chewing is a well-known risk factor for oral cancer in the Asian population. However, there is currently little evidence on the intergenerational psychosocial transmission of paan chewing in South Indian families.

Purpose: To investigate the association between parental and participant's paan chewing in a South Indian population.

Methods: A subset of data was drawn from a hospital-based case-control study, HeNCe Life study, conducted at Government Dental and Medical Colleges of Kozhikode, South India. Analyses were based on 371 non-cancer control participants having diseases unrelated to known risk factors for oral cancer, frequency-matched by age and sex to oral cancer cases. Information pertaining to demographics, behavioural habits (e.g., paan chewing, smoking), and indicators of socioeconomic position(SEP) of both participants and their parents was collected with the use of a questionnaire-based interview and a life grid technique. Paan chewing was measured as a categorical variable as "ever chewer" (at least one year of usage) and "never chewer". Data analysis included descriptive statistics, and unconditional logistic regression to assess odds ratios (OR) and 95% confidence intervals (95%CI) for the associations between parental and participant's paan chewing, adjusted for confounders.

Results: Over half of the participants were male (55.17%) with a mean age of 59(SD=12) years. After adjusting for age, religion, parents' SEP, parents' education, smoking and alcohol consumption, perceived parenting behaviours, maternal and paternal PCH were significantly associated with participant's paan chewing (OR=2.40,95%CI=1.11–5.21) and (OR=3.05, 95%CI=1.48–6.27), respectively.

Conclusion: Intergenerational psycho-social transmission of the habit of paan chewing could occur through shared socio-cultural or environmental factors. Multigenerational psycho-social intervention should be considered for effective prevention of this habit.

Introduction

The ability to learn skills from older generations plays a crucial role in cognitive evolution. A child uses these abilities to learn about society and unexpected behaviours. This learning ability by observing others is part of the premises of social learning theory(190). Differential association (direct and indirect interaction), differential reinforcement (learning through rewards and punishment), imitation (learning by observation) and cognitive definition(attitudes) are the main mechanisms by which this learning process occurs(191). Through generations, these mechanisms help to develop a shared cultural intelligence, which determines the acceptable and unacceptable behaviours in a society(192). Social learning theory has been used to explain many characteristics of accruing social behaviours including smoking, alcohol abuse and deviant behaviours(98,193).

Tobacco use, a well-established aetiological factor for oral cancer, is a highly prevalent habit in India. By 2020, mortality related to this habit is expected to rise to more than 1.5 million annually in this country alone(91). Smokeless tobacco is the most common form of tobacco use; over 26% of the Indian population consumes it(23). Paan (betel quid with or without tobacco) is one of the most prevalent forms of smokeless tobacco, with 49.7 million (8%) of users in the country(23). Although the components of the paan may vary according to geographical area, it is usually a mixture of areca nut (from the areca catechu tree), slaked lime (calcium hydroxide) with or without tobacco, wrapped in a piper betel leaf(85). The prevalence of paan chewing, the strongest oral cancer risk factor in India, is increasing among the youth in this population(194). The International Agency for Research on Cancer (IARC) has classified betel quid with or without tobacco as a human carcinogen (Group 1)(3,85,195).

A recent systematic review on the social context of smokeless tobacco use showed that the mean age of initiation was 15 years. The reasons for starting the habit included social and cultural acceptance, low cost and easy availability, peer pressure, taste, and mental relaxation effects(93).In addition, the most common social context of tobacco chewing was paan use by a family member. Qualitative

studies also showed the cultural acceptability of the habit(93). Although parental influence and the contribution of parenting behaviour patterns to smoking(98,109,119,196,197) and alcohol habits(101,102,115,119,198–200) have been widely investigated, the intergenerational transmission of paan chewing habit has received less attention(106–108,201). In addition, most of the studies had methodological limitations. For example, they were limited to descriptive analyses and often used a simplified conceptual framework without accounting for potential confounders(106–108,201). Furthermore, none of them explored how parenting behaviours can modify the association between parental paan chewing and their offspring's paan chewing, which is considered crucial in mediating intergenerational continuity of risk taking behaviours(112). Lastly, none of the previous studies investigated maternal and paternal habits separately. Unlike Western cultures where most of such studies were conducted, India has more interdependent family dynamics with a highly patrilineal society(202). Therefore, it is important to understand the gender roles in this transmission. In this paper, we investigate the association between each of maternal and paternal paan chewing habits and the subject's paan chewing. Furthermore, we explore whether this association is modified by the parenting behaviour patterns.

Materials and methods

Study design

This paper uses data pertaining to the control participants of a hospital-based case-control study investigating the aetiology of cancer in the upper aero digestive tract. In brief, the HeNCe Life Study was conducted at the Government Dental and Medical Colleges of Kozhikode, South India from 2008 to 2012. Cases, were newly diagnosed and histologically confirmed oral squamous cell carcinoma (N=350). Control participants were non-cancer subjects (n=371) recruited from outpatient clinics of the same institutions as the cases, and were frequency-matched to cases by age and sex.

The eligibility criteria were: (i) to be born in India; (ii) to be at least 18years of age; (iii) to live within 150km of the hospital area; and (iv)to have no previous

history of cancer or HIV infection. The study was approved by the Institutional review boards of all participating institutions.

Data collection

After obtaining written informed consent, trained dentists collected information during a questionnaire-based interview using a life grid technique(165). Fieldwork operations, including the research instruments, were tested in a pilot study conducted during 2007-2008, and modifications were made accordingly. Detailed information was collected on indicators of socioeconomic position (SEP), psychosocial, and behavioural factors along the participant's life span. For subjects who had difficulty speaking due to their disease (14.3% cases, 3.5% controls), interviews were conducted with the help of a proxy, usually a close family member.

Data reduction for perceived parenting behaviour

Participants' perception of their mother's and father's parenting behaviours were recorded using a modified version of the parental bonding instrument(120)(7 questions), adapted from the Whitehall study II(170). Internal consistency of these questions was assessed using Cronbach's alpha value. To identify the latent constructs these questions were measuring, an exploratory factor analysis was carried out separately for maternal and paternal parenting behaviours. An oblimin rotation with delta 0 was applied and factors with an Eigenvalue > 1 were retained. Two latent constructs of subject's perception of parenting behaviours were identified for each parent, resulting in four variables: maternal warmth, maternal strictness, paternal warmth and paternal strictness. Four questions regarding understanding, loving, affectionate and trustworthy behaviour of the parent loaded on the warmth factor, and two questions regarding punishment and rules loaded on the strictness factor. For better interpretability of the scores, the questions were combined based on their factor loadings (refer section 6.1). These scores are higher when the parental warmth or strictness is higher.

Statistical analysis

Information on each parent's paan chewing was collected as 'never' or 'ever chewer' of paan (at least one year of habit history). Participant's complete history of paan chewing was collected. The presence or absence of habit was considered as the outcome of interest where also using at least one year of paan chewing was used to classify subjects as 'ever chewers'. Level of education was collected as years of education and then categorized based on the historical context of Kerala , the study site (173). For participants born until 1950, more than four years of formal education was considered as a high educational attainment, whereas the same category was attributed to those with more than eight years of formal education for participants born after 1950.

Lifetime history of smoking and alcohol consumption were collected, and later categorized as 'never or ever user'. Parent's SEP was assessed using 9 questions about participant's childhood material adversities (housing conditions and amenities). Further, responses to each question were dichotomized, considering the presence or absence and material cost, as denoting high or low material deprivation. These variables were then combined into an index by adding the scores of material deprivation resulting in values ranging from 0 to 9. The index was further categorized into low and high SEP using the median as a cut-off point.

Fifty-one (16%) participants had missing values in maternal or paternal education and one subject had missing information for paternal paan chewing. Multiple imputation by chained equation (MICE) was carried out to impute missing values; 20 imputed data sets were generated and "Rubin's rules" were applied to combine estimates of interest across the imputed data sets(179). The missing value for paternal paan chewing was not imputed, this subject was excluded from the analysis.

Causal diagrams are a visual representation of the causal relationships between variables in a source population. Directed acyclic graphs (DAG) are a type of causal diagram introduced by Pearl in 1995(183). DAGs based on *a priori* knowledge, are widely used to help plan data collection and analysis, in communicating results and to avoid pitfalls when selecting confounders(184,185). We used DAGs to identify the minimum set of confounders to be taken into account to estimate the true association between parental and participant's paan chewing (Figure 6-1 &6-2).

Figure 6-1: Directed acyclic graph of association between maternal and participant's paan chewing habit.

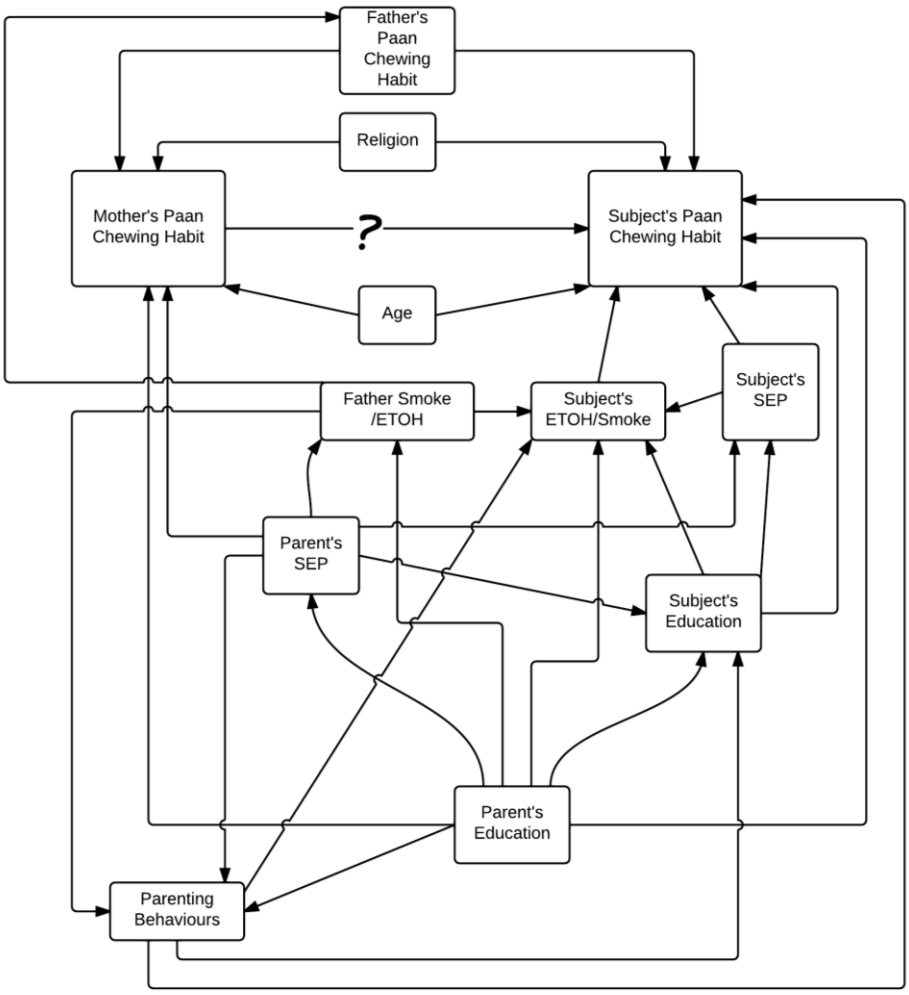
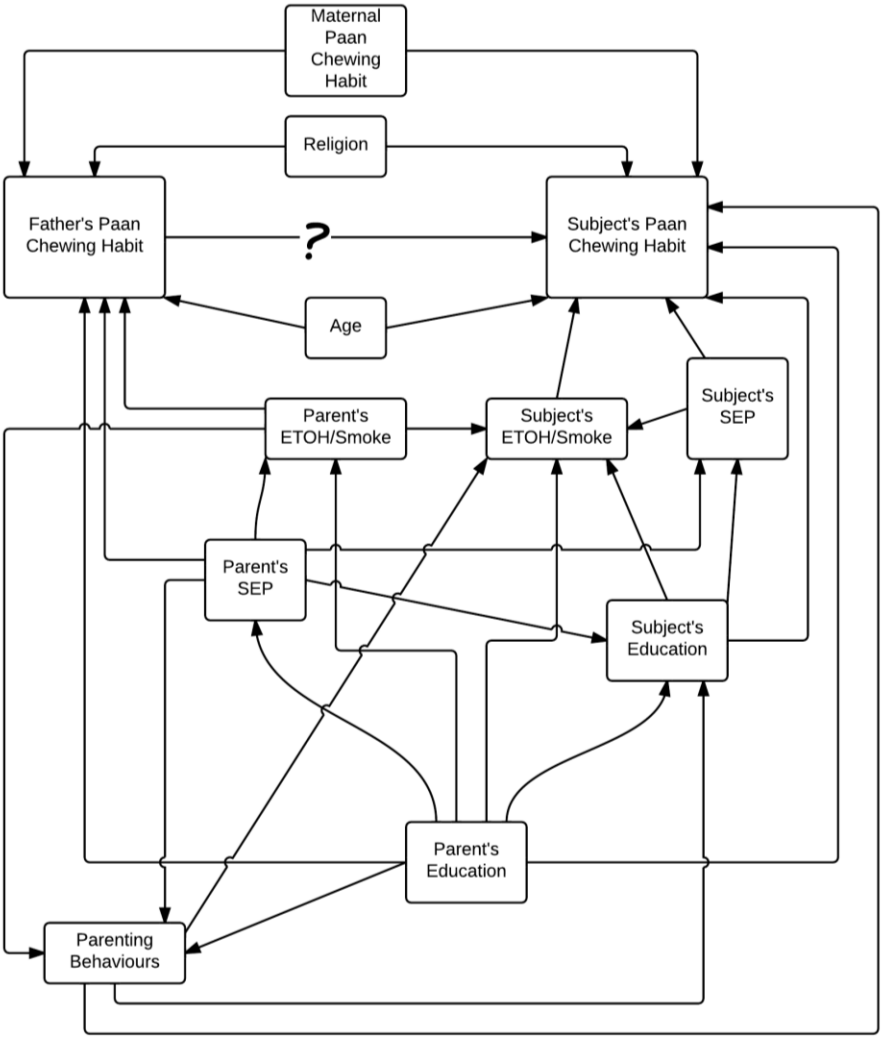


Figure 6-2: Directed acyclic graph of association between paternal and participant's paan chewing



Age, religious beliefs, parent's SEP, and perceived parenting behaviour were identified as the minimum set of potential confounders, to be included in the multivariate analyses. Further, to separate the effect of maternal and paternal paan chewing, they were mutually adjusted for one another in the corresponding models.

Data analyses included descriptive statistics, and unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95%CI) for the associations between parental and participant's paan chewing. All the analyses

were carried out using STATA-12 (StataCorp LP, College Station, Texas, USA) (182).

Because the hypothesised psychosocial transmission of paan chewing from parents to the participant assumes that the participants were raised by their parents during childhood through adolescence, subjects who reported that they were not brought up by their parents (n=52, 14.0%) were excluded from the analysis.

Results

We explored the representativeness of the final sample by comparing our results to a recent survey published on the source population (Table 6-1).The prevalence of paan chewing in both samples was similar, denoting adequate representation in regards to exposure of interest. Table 6-2 displays the frequency distribution of selected variables in our sample. Participants' age ranged from 29 to 89 years with a mean age ± SD of 59.86 ± 11.8years (Table 6-2). More than 55% of the participants were males and 52(16.3%) reported the habit of paan chewing for at least one year. The majority were Hindus (61.0 %) and literate (86.2%). Parental paan chewing was more prevalent among participants who were paan chewers: 76.9% and 61.5% of paan chewers reported that their mother and father had the habit, respectively (Table 6-3).

Table 6-1: Frequency distribution of paan chewing in the HeNCe Life study (India: 2008-2012) and Global Adult Tobacco Survey (GATS) (India: 2009-2010)

	HeNCe (%)	**GATS (%)**
Age range in years	29 to 89	15 and above
Sex		
Males	55.2	51.7
Females	44.8	48.3
Participant's paan chewing		
Never users	83.7	86.5
Past users	6.9	2.8
Current users	9.4	10.7

Table 6-2: Frequency distribution of selected potential confounders among control participants of the HeNCe Life study, Kerala, India (2008-2012)

	N (%)[1]	Missing (%)[2]
Participant's measures		
Mean age ± SD, years	59.86 ± 11.8	
Religion		
Non-Hindu	124 (39.0)	
Hindu	194 (61.0)	
Education		
Low education	149 (46.9)	
High education	169 (53.1)	
Smoking		
Never	185 (58.2)	
Ever	133 (41.8)	
Alcohol consumption		
Never	263 (82.7)	
Ever	55 (17.3)	
Parental measures		
Maternal education		42 (13.2)
No formal education	172 (62.3)	
At least one year of formal education	104 (37.7)	
Paternal education		48 (15.1)
No formal education	117 (43.3)	
At least one year of formal education	153 (56.7)	
Parent's socioeconomic position		
Low SEP	145 (45.6)	
High SEP	173 (54.4)	
Maternal warmth index, mean ± SD	13.77 ± 2.2	
Maternal strictness index, mean ± SD	4.09 ±1.4	
Paternal warmth index, mean ± SD	11.98 ±3.0	
Paternal strictness index, mean ± SD	4.58 ±1.6	

[1]Percentages, unless otherwise specified, among all valid responses
[2]Percentages, unless otherwise specified, among all subjects included in the current analysis (n=318)

Table 6-3: Associations between parental and participant's paan chewing habits

	Participant's Paan chewing		Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Fully adjusted OR (95%CI)
	Never N= 266 N (%)	Ever N= 52 N (%)			
Maternal PCH					
Never	155 (58.3)	12 (23.1)			
Ever	111 (41.7)	40 (76.9)	4.65 (2.26 – 10.16)	2.66(1.25 – 5.65) [1]	2.40 (1.11 – 5.21)[2]
Paternal PCH					
Never	190 (71.4)	20 (38.5)			
Ever	76 (28.6)	32 (61.5)	4.00 (2.06 – 7.84)	2.93 (1.44 – 5.95)[3]	3.05 (1.48 – 6.27)[4]

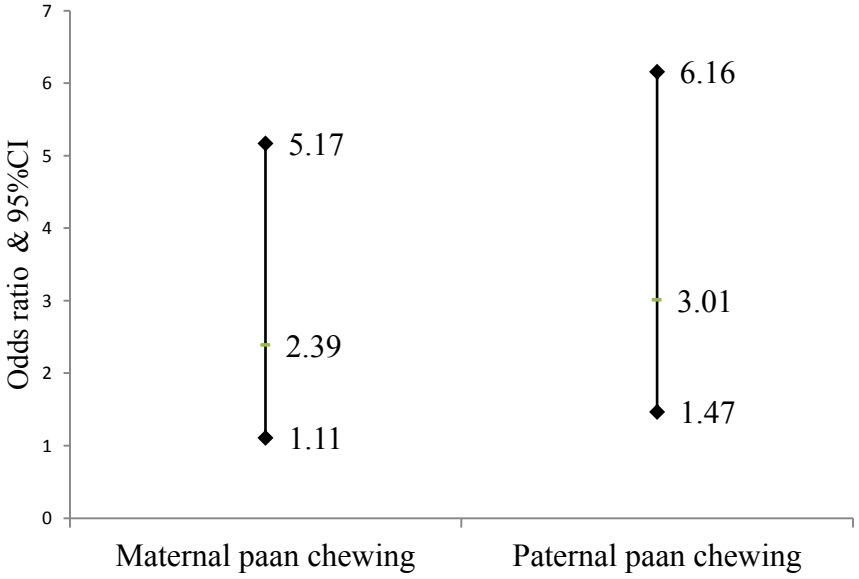
[1]Adjusted for age, religion, maternal and paternal education, parent's SEP and paternal paan chewing
[2]Further adjusted for maternal warmth and maternal strictness
[3]Adjusted for age, religion, parent's levels of education, smoking, alcohol use, parent's SEP and maternal paan chewing
[4]Further adjusted for paternal warmth and paternal strictness

After adjusting for the paternal paan chewing, subjects who had mothers with paan chewing habit were2.4 times more likely to have adopted the habit compared to subjects whose mothers were not paan chewers [OR=2.40,95% CI:1.11 – 5.21]. Similarly, after adjusting for maternal paan chewing, subjects who had fathers with the habit of paan chewing were 3 times more likely to be chewers compared to others [OR=3.05,95% CI: 1.48 – 6.27] (Table 6-3). Perceived maternal strictness was significantly associated with participant's habit of paan chewing [OR= 1.34, 95% CI: 1.05 – 1.70], whereas perceived maternal warmth had only a marginally significant effect [OR= 1.15, 95%CI: 0.97 – 1.35]. Perceived paternal warmth and strictness were not significantly associated with participant's habit of paan chewing ([OR= 1.05, 95% CI: 0.93 – 1.18] and [OR= 1.00 95%CI: 0.80 – 1.27] respectively).

Discussion

This study investigates the associations between parental and participant's paan chewing habits, and explores the association between perceived parental behaviour and participant's habit of paan chewing. In doing so, this study adds to the literature by examining psychosocial intergenerational risk transmission in relation to paan chewing. This topic has been widely studied in the Western world in regard to transmission of alcohol abuse, smoking, adolescent delinquency and other anti-social behaviours, where parenting styles have been proposed to have a mediating and reinforcing effect(98,101,102,119,170,196,203). Our results suggest that maternal and paternal habit of paan chewing have an effect on the participant's habit among subjects attending outpatient clinics of hospitals located in Kerala. Moreover, maternal and paternal contributions to the intergenerational risk transmission were similar (figure 6-3). However; maternal strictness was significantly associated with participants' habit of paan chewing even after adjusting for maternal paan chewing. Whereas, other measures of parental behaviours were not significantly or only marginally associated with the participant's habit of paan chewing.

Figure 6-3: Association between parent's and participant's paan chewing



Although a hospital based study design limits the external validity of our results, our sample was representative of the source population in regards to paan chewing habit based on a recent population survey(Table 6-1)(23). There was only a single level of measurement in our study, that is, participants described their parents' habits and not the parents directly, but we adopted a life grid technique to collect data within a life course framework and this technique has been shown to reduce recall bias(165). Cross sectional study results have lower potential in explaining causality or association due to difficulty in establishing the temporal sequence of events, but there is no reason to expect that the current paan chewing status of the participant could affect the differential recall of their parental habit. Even though biological causality cannot be judged, what is more meaningful, from a knowledge translation point of view is that our results show the psychosocial risk for an intergenerational continuity of the habit of paan chewing in a subgroup of individuals. This intergenerational continuity may result from a process by which one generation leads the subsequent generation to a disadvantaged life trajectory(112).

Biological influence through genetic materials kept aside, the parent and offspring may have multiple shared social, cultural, lifestyle and environmental experiences which kick start the cycle of risk taking behaviours through generations.

This is the first study to our knowledge to empirically investigate the association between perceived parental behaviours and participant's habit of paan chewing in India. One aspect of this relationship is the parenting style. Although our questionnaire is validated and derived from the parental bonding instrument(170), it was not specifically designed to measure parenting style. Nevertheless, it can provide insights into this important aspect of parent-child relationships. The mediation role of parenting styles has been well documented in the intergenerational continuity of smoking and alcohol(108,113,116,199). Most studies were conducted in Western populations, where authoritative parenting style is more common which allows the child greater independence. However, the authoritarian parenting style is more common in India, which is less flexible and includes strong discipline practices(202).

Socio-cultural context and family dynamics in India differ from those in the Western world. Indian families are more interdependent compared to the Western autonomous lifestyle(204). Child rearing practices are also different; more parental control is considered as protection rather than constraint(202), and discipline practices extend to a social acceptance of corporal punishment (spanking and slapping)(205). In a hierarchical society such as India, there is a strict adherence to gender roles where a notion of a strict father and a kind mother has been documented(206). This observation supports our results showing that maternal strictness, which included questions on punishment and enforcement of rules, is significantly associated with the participant's habit of paan chewing. High maternal strictness may have negatively affected the child's psycho-social development contributing to paan chewing later in life.

Research has proposed a conceptual framework exploring reasons for starting paan chewing among adolescents(207), but this framework has not been tested. Three main intergenerational psychosocial transmission processes have been proposed: 1) Role modeling by children – children try to imitate their parent

which may lead to addiction; 2) Socialization of the child by the parent – parent-child interaction, social reinforcement, familial norms, easy access to the substance and parenting styles; 3) Genetic predisposition(109).

Looking at transmission of behaviour has the advantage of targeting modifiable factors as opposed to looking only at intergenerational transmission of genetic factors because behaviours are partially chosen while genes are not. Also, if compared to the transmission of education, intergenerational transmission of behaviour is less affected by family socioeconomic circumstances. Parental behaviour is crucial for its consequences on the development of children's behaviour resources along their life(99).

One of the pathways through which children acquire behaviours from their parents is explained by social learning theory(190). The child can initiate the habit by direct or indirect interaction with a parent. When children observe their parent's chewing paan, they may indirectly perceive the psychological and physiological rewards of the habit and this, coupled with children's natural tendency to imitate parents, can lead to initiation of the habit of paan chewing. At this phase, parental reinforcement can modify the child's behaviour; when the negative reinforcement is absent, the child assumes that the habit is acceptable in the family(191).

A recent systematic review on the social context of smokeless tobacco use summarized the themes which evolved from different qualitative studies assessing determinants of initiation. These themes explain other socio-cultural determinants, including familial positive norms and misbelieves about beneficial effects of paan, as well as using children to purchase tobacco products for elders in the family which may induce curiosity and lead them to experimentation(93). All these processes are valid in paan chewing, but more longitudinal, genetic and qualitative studies are needed to fully understand these complex processes.

Knowledge translation

Our results show that both the association of maternal and paternal habit of paan chewing with participant's paan chewing were statistically significant and similar. Moreover, only maternal strictness had a significant association with participant's paan chewing; this is understandable in a South Indian context where children are emotionally closer to their mother than to their father(208). These results may have a significant impact on policy development. Indeed, more effective targeted interventions could be planned by identifying high risk population and including parents in the school-based programs, thereby interrupting the intergenerational transmission of the habit of paan chewing. Similar interventions have been shown to be effective in the field of smoking prevention, where school based buddy programs resulted in reducing smoking not only among kids but also their parents(209). Furthermore, studies have shown that the adolescent perceived such interventions as highly motivating(210).

Mass media campaigns tapping into the morality of a responsible parent have been taken up in many countries in regards to smoking, alcohol abuse and even road traffic awareness(207,208). Similar campaigns could be effective in breaking the role modeling and socializing process in the intergenerational transmission of paan chewing habit.

This study investigated maternal and paternal contributions to the intergenerational psychosocial transmission of paan chewing among South Indian subjects. The results suggest that the parental habit of paan chewing is a component of the complex shared social, genetic and environmental factors that contribute to an individual's paan chewing. Our findings support the need for multigenerational psychosocial intervention for effective prevention of paan chewing in this population.

6.1 Additional analysis to manuscript – I

To identify the latent constructs measured through a modified version of the Parental Bonding Instrument (PBI), an exploratory factor analysis(171) was carried out separately for maternal and paternal parenting behaviours. An oblimin rotation with delta 0 was applied and factors with an Eigenvalue > 1 were retained.

Internal consistency of the instrument was assessed using Cronbach's alpha (213). An alpha value between 0.7 to 0.8 shows satisfactory internal consistency of the instrument tested(214). In our study both maternal and paternal parental bonding questionnaire showed satisfactory internal consistency (0.754 for maternal and 0.805 for paternal questionnaires). Cronbach's alpha values tend to be low if the number of questions is less or if they are measuring multiple dimensions(213). We used a modified version of PBI with only 7 questions for each parent whereas the original PBI has shown to be measuring more than one dimension of parental bonding(125,215). This may be one reason for moderate level of internal consistency of our instrument.

Table 6-3 shows the rotated pattern matrix for maternal and paternal instruments respectively. Both of them showed adequate Kaiser-Meyer-Olkin measure for sampling adequacy (0.731 for maternal and 0.805 for paternal instrument)(216). Only two factors had an Eigenvalue >1 for each parent. The combination of two factors explained for 65.3% and 73.8% of the variance in maternal and paternal measures respectively. The factor loadings were assessed using rotated pattern matrix and factor loading plots (Figure 6-4& 6-5). All except two measures, (maternal (M7) and paternal expectation (F7)), where heavily loading heavily on either of the two latent factors.

To better interpret the latent constructs these two variables were dropped for further analyses. Measures loading on the same factor were combined together through simple summation to compute 'warmth' and 'strictness' variables for each parent. Although this is a non-refined method of creating factor scores, it has shown to be stable across different samples(217).

Table 6-4: Rotated factor loadings (pattern matrix) of maternal& paternal bonding measures.

Item	Factor 1* (Warmth)	Factor 2* (Strictness)
Maternal		
M1 – How much did she understand your problems and worried?	0.8283	
M2 – How much could you confide in her about things that were bothering you?	0.7058	
M3 – How much love and affection did she give you?	0.8471	
M4 – How much time and attention did she give you when you needed it?	0.8264	
M5 – How strict was she with the rules for you?		0.8676
M6 – How harsh was she when she punished you?		0.8286
M7 – How much did she expect you to do your best in everything you did?	0.5664	
Paternal		
F1 – How much did he understand your problems and worried?	0.8396	
F2 – How much could you confide in him about things that were bothering you?	0.8275	
F3 – How much love and affection did he give you?	0.8824	
F4 – How much time and attention did he give you when you needed it?	0.8614	
F5 – How strict was he with the rules for you?		0.8979
F6 – How harsh was he when he punished you?		0.9013
F7 – How much did he expect you to do your best in everything you did?	0.7435	

*factor loadings <0.4 not shown

Figure 6-4: Factor loading plot for maternal bonding measures

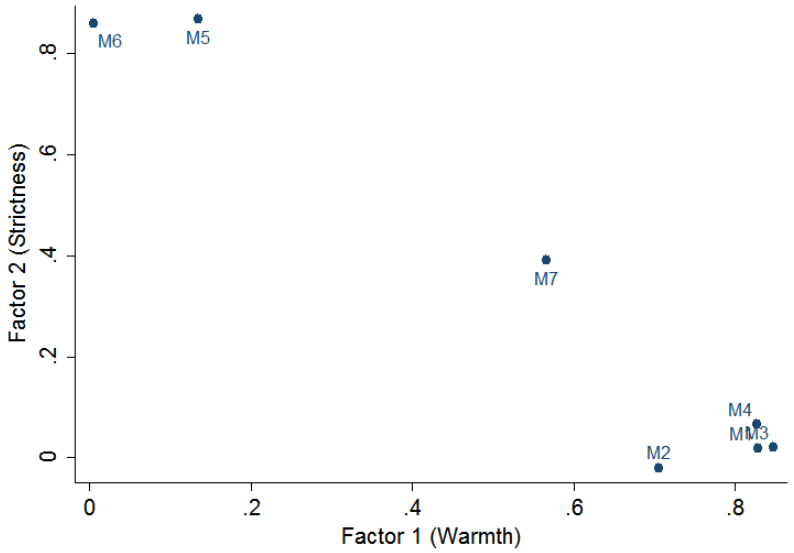
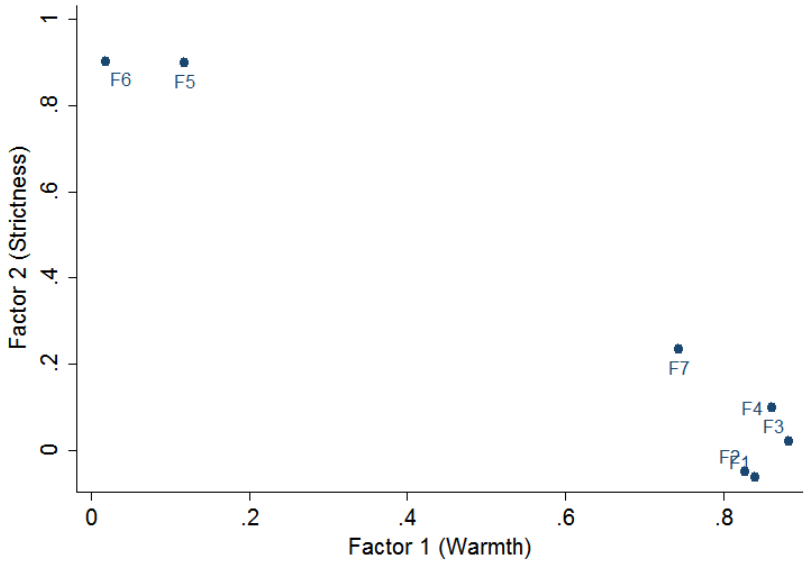


Figure 6-5: Factor loading plot for paternal bonding measures



7. MANUSCRIPT – II

Dose-response relationship between paan chewing habit & risk of oral cancer: Restricted cubic spline regression analysis

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Abstract

The association between paan-chewing and oral cancer risk is well documented. Although studies have shown a significant dose-response relationship between this habit and oral cancer, most adopted categorical trend analysis. Regression spline models offer an alternative that circumvents the forced assumption of linearity and disadvantages associated with categorisation of exposure.

Objectives: To estimate the dose-response relationship between paan chewing and risk of oral cancer in a subset of a South Indian population.

Methods: In a hospital-based case-control study, the HeNCe Life study-India, incident cases (n=350) of oral squamous cell carcinoma were recruited from 2 major public teaching hospitals in Kozhikode, India. Non-cancer controls (n=371), frequency-matched by age and sex, were recruited from different outpatient clinics of the aforementioned hospitals. Data on socio-demographic and behavioural factors were collected using a questionnaire and the life-grid technique. Lifetime exposure to paan was computed as 'chew-years', one chew-year being equivalent to chewing one quid of paan every day for one year. We used descriptive statistics and restricted cubic spline logistic regression to test dose-response relationships.

Results: The majority of the oral cancer cases had the habit of paan chewing (72%) compared to the controls (18%). A nonlinear dose-response relationship was observed between cumulative chew-years of paan and risk of oral cancer. The risk increased steeply at low doses and a plateauing of risk occurred at high exposures (>470 chew-years). Years since cessation were not significantly associated with risk of oral cancer.

Conclusion: This is, to our knowledge, the first time that a nonlinear dose-response relationship between paan chewing and oral cancer is observed in an Indian population. Clinically, these results could be used in behaviour counselling demonstrating risk associated even with low doses and justifying risk reduction measures.

Introduction

Oral cancer is a debilitating disease with more than 2.6 million affected individuals worldwide(14). More prevalent in south-central Asia and Melanesia than the rest of the world, the 2010 age-standardised mortality rate from this cancer in India was 22.1 and 9.4 deaths per 100,000 among men and women respectively(15). This number is predicted to rise; the projected estimate of oral cancer incidence in India by 2020 is more than 2 million(17). A major cause of this high incidence is the high prevalence of the habitual chewing of paan; more than one fourth of the population in India practices this habit(23).Paan is a colloquial name of a mixture of areca nut (nut of a palm tree – *areca catechu*), slaked lime (calcium hydroxide), and betel leaf (leaf of piper betel vine) with or without tobacco(1). Carcinogenicity of paan chewing has been well established(3).

Several studies have reported a positive dose-response relationship between paan chewing and oral cancer(22,71,218–222). However, all except one(222), followed a categorical trend analysis known to present several limitations(140,156). Some of these limitations include the biologically implausible jump in estimated risk at the intersection of two categories due to the forced assumption of linearity with a category, and the results are to the influence of the choice of cut off points used for categorization.

Restricted cubic spline regression is a flexible modeling technique proposed as an alternative to traditional trend analyses, in which linearity does not have to be assumed. It circumvents the disadvantages associated with the trend analysis (145,156). The only study in which flexible modeling techniques were implemented for estimating dose-response curve of paan chewing investigated chewing betel quid without tobacco, the most prevalent form in Taiwan(222). The authors found a curvilinear dose response between this habit and risk of oral cancer(222). Both tobacco and betel quid without tobacco, have been classified as human carcinogens(Group 1) by the International Agency for Research on Cancer (IARC) and could have synergistic effects(3). Moreover, tobacco is often an ingredient of paan in India(23).

Previous studies took into consideration only one dimension of the habit (frequency or duration), whereas it is well understood from the field of lung cancer and smoking that these dimensions are interrelated and should be modeled together to estimate the true relationship(186). Moreover, effect of years since cessation of habit was not considered which may have led to some amount of residual confounding.

Hence, through a subset of the South Indian population we estimate the dose-response relationship between lifetime cumulative exposure to paan chewing and risk of oral cancer; further, we investigate the association between years since cessation of the habit and risk of oral cancer.

Methods

The data was drawn from a hospital based case-control study – HeNCe Life Study India, conducted from 2008 to 2012 at the Governmental Dental and Medical Colleges of Kozihode, South India. The cases (n=350) were newly diagnosed histologically confirmed oral squamous cell carcinoma, which included malignant neoplasm of oral cavity based on International Statistical Classification of Diseases and Related Health Problems10th revision (ICD-10): codesC00.3-C06.9, C09. Controls (n=371) were non-cancer patients with diseases unrelated to tobacco or alcohol consumption reported at different outpatient clinics of the aforementioned hospitals during the same time period. Controls were frequency-matched with cases according to age (5 year age groups) and sex.

The general inclusion criteria for participants were (i) born in India; (ii) at least 18 years of age; (iii) no previous history of cancer, HIV infection or mental disorders, and; (iv) living within 150 km from the site.

Data collection

Data collection was done by three professionally trained dentists using a structured questionnaire with the help of a life grid technique (164). Information on age, sex, education, material deprivation, vegetables consumption, oral hygiene and dental caries experiences were collected.

Comprehensive lifetime histories of behavioural risk factors (tobacco smoking, alcohol consumption, and paan chewing) were also collected, as periods of same frequency of use and type of product (brand of cigarette or type of paan and alcohol).

Paan chewing habit

In India tobacco is usually included in paan, and hence some studies categorise the product under smokeless tobacco. The practice of not providing a proper definition of exposure in studies pertaining to paan chewing makes it difficult to compare results across studies and populations(85). However, ingredients of paan and preferred combinations of ingredients change according to personal preferences and geographical availability, making it impossible to adopt a standard definition. Moreover, the same person can use different combinations at different points in their life, which reduces the value of separately investigating exposure to each combination.

Hence, we adopted as a working definition of paan in our study, any combination which included areca nut, tobacco or both since these two major ingredients are known to be human carcinogens(3). Participants reporting at least one year of the habit were considered as ever paan chewers. Those who had stopped at least one year prior to the date of interview were considered as past chewers.

A summary measure for lifetime exposure was computed from the participant's complete paan chewing habit history, and expressed in chew-years, One chew-year is equivalent to chewing one quid, or portion, of paan every day for one year. Due to potential problems of multicollinearity, the use of a summary variable similar to chew-years was preferred over duration and frequency separately while adjusting for time since cessation in the same model(186). For past chewers, years since cessation (quit-years) were computed as the difference between age at quitting of habit and age at diagnosis (cases) or interview (control).

Covariates

Continuous lifetime exposure was also computed for cigarette, bidi smoking (pack-years), and alcohol consumption (number of standard drinks – 18 ml of

pure ethanol – per week). Ever/past smoking and alcohol drinking were defined in the same manner as for paan chewing.

Material deprivation measured through housing conditions is considered as an indicator of an individual's socio-economic position(52). We measured housing conditions during three different periods of life (before 16 years, 17-30 years and after 30 years). Different measures of housing conditions at each of these stages were dichotomized in to low or high levels of material deprivation based on the presence or absence of amenities (e.g., toilet inside the house) and cost and type of the material (e.g., type of material used to build the house). A continuous material deprivation index was computed at each stage by summing these binary measures. These indices were further categorized as low and high levels of material deprivation based on the median value among control participants. Finally, a lifetime cumulative indicator of material deprivation was created depending on the number of periods spent in high level of material deprivation. There were four categories for this variable: (i) all three life periods spent in high level of material deprivation; (ii) 2 life periods in high and one in low level of material deprivation; (iii) one life period in high and 2 periods in low level of material deprivation, and;(iv) all three periods of life in low material deprivation.

Oral hygiene and dental caries experiences measured by the DMFT (decay-missing-filled-teeth) index were evaluated in a dental clinical setting with the use of mouth mirrors and adequate light source. Average frequency of consumption of vegetables (e.g., tomato, carrot, cabbage, cauliflower, pumpkin, spinach,) per week, until 2 years prior to the date of diagnosis or interview was also used as continuous variable.

Statistical analysis

The outcome variable was defined as oral cancer case or control status. Descriptive statistics were performed to explore the data. All multivariate analyses included the following *a priori* confounders: age, sex, pack-years of bidi, pack-years of cigarette, drinks per week of alcohol, number of missing teeth, indicator of material deprivation and weekly vegetables consumption.

To account for the qualitative difference between never, current and past chewers of paan a 3-category indicator variable was included in the model. Adjusting for this variable allows us to interpret the coefficient of continuous variables as the estimate of the quantitative effect of these factors among current or past chewers accordingly. Chew-years and years since quitting paan variables were centered by subtracting their respective means from the observations for ever chewers of paan while attributing a value of zero for never chewers. This linear transformation does not modify the regression coefficients for continuous variables(187), but ensures that the measure of effect of the indicator variable compares a current chewer with mean amount of chew-years - or a past chewer with mean amount of chew-years and quit-years to a never chewer.

We established the association between paan chewing and oral cancer through an unconditional logistic regression model, where the exposure of interest was a binary variable of paan chewing (ever or never chewer). Then the dose-response relationship was investigated using restricted cubic spline logistic regression (144,145) and pointwise 95% confidence intervals(CI) were calculated.

Five different models with increasing number of knots (3, 4, 5, 6 and 7) were tested.

The position of knots was chosen from percentiles of chew-years among ever chewers using a modified version of Harrell et al.'s recommendation of placing knots at equally spaced percentiles(188). The knots' positions were as follows: 3 knots – 5^{th}, 50^{th}, 95^{th} percentiles; 4knots – 5^{th}, 35^{th}, 65^{th}, 95^{th} percentiles; 5knots – 5^{th}, 27.5^{th}, 50^{th}, 72.5^{th}, 95^{th} percentiles; 6knots – 5^{th}, 23^{rd}, 41^{st}, 59^{th}, 77^{th}, 95^{th} percentiles; 7knots – 5^{th}, 20^{th}, 35^{th}, 50^{th}, 65^{th}, 80^{th}, 95^{th} percentiles.

Model fit was assessed using Akaike's information criteria(146). A likelihood ratio test was performed between the linear model and the best-fit model to determine whether the best-fit model was significantly different from the linear model. The dose-response curve was interpolated using the spline parameters from the best-fit model. All analyses were done with STATA12 for Windows (StataCorp, Texas, USA)(182).

There were missing values only for the lifetime material deprivation indicator. Because the percentage of missing data was low, we can consider a complete case analysis(188). Thus, analyses excluded 35 (4.85%) participants (16 controls (4.31%) and 19 cases (5.43%)), resulting in a sample size of 686 participants (331 cases and 355 controls).

Results

Table 7-1 presents the distribution of *a priori* confounders of the association between paan chewing and oral cancer. Mean age of participants was around 60 years and not significantly different between cases and controls. Except for age, sex and vegetable consumption, all the other variables were significantly associated with risk of oral cancer in the univariate analyses. The paan chewing habit was significantly more prevalent among cases than controls. Only 17.7% of controls had ever chewed paan as compared with 72.5% of cases (Table 7-2). In the univariate analyses among ever chewers of paan, cancer cases had significantly higher mean lifetime chew-years as compared with controls (p= 0.046), however no significant difference was observed in the distribution of years since cessation (p=0.079) (Table 7-2).

Table 7-1: Frequency distribution of selected confounder variables in dose-response relationship between paan chewing habit and risk of oral cancer

	Controls	**Cases**	**P value**
	n= 355	**n=331**	
	n(%)	**n(%)**	
Sex			
Female	165 (46.5)	149 (45.0)	
Male	190 (53.5)	182 (55.0)	0.701
Lifetime material deprivation			
3 low	77 (21.7)	15 (4.5)	
2 low, 1 high	75 (21.1)	33 (9.9)	
2 high, 1 low	80 (22.5)	64 (19.3)	
3 high	123 (34.7)	219 (66.2)	< 0.001
	Mean ± SD	**Mean ± SD**	
Age	60.52 ± 11.4	60.79 ± 11.3	0.753
Bidi (pack-years)	4.39±13.4	8.68±17.2	0.001
Cigarette (pack-years)	9.89±25.7	6.19±17.0	0.028
Alcohol (standard drinks per week)	1.33±7.2	6.69±34.7	0.005
Missing teeth	9.98±10.6	11.92±10.6	0.017
Vegetable consumption (weekly frequency)	12.69±4.0	12.23±3.7	0.114

Table 7-2: Distribution of different dimensions of paan chewing among oral cancer cases and controls

	Controls (n=355) n (%)	Cases (n=331) n (%)	P value
Paan chewing habit			
Never chewers	292 (82.3)	91 (27.5)	
Current chewers	36 (10.1)	131 (39.6)	
Past chewers	27 (7.6)	109 (32.9)	< 0.001
Life time exposure variables among ever chewers of paan	**n = 62**	**n = 240**	
Chew-years	211.41±208.4	266.96 ± 191.1	0.046
Quit-years	4.56 ± 9.8	2.83 ± 5.9	0.079

In the multivariate model to estimate the association between paan chewing and oral cancer, ever chewers of paan had a 13-fold higher risk of being diagnosed with oral cancer compared to non-chewers (OR = 13.37; 95% CI = 8.66 – 20.64).

Dose-response relationship

We tested 5 different restricted cubic spline regression models with an increasing number of knots; Table 7-3 presents the AIC values of the different models. All restricted cubic spline models had lower AIC values compared to the linear model, denoting a better fit to the data than the conventional linear model.

Burnham et al. showed that a difference of less than two points in AIC values may not be considered as an improvement in the model fit(223). Based on this widely used cut off, out of the three models with lowest AIC values the 3 knots model was chosen as our final model. Moreover, dose-response curves estimated from observational studies should be simple in shape (141), due to the limitations of observational data compared to experimental data. Hence, it is desirable to be

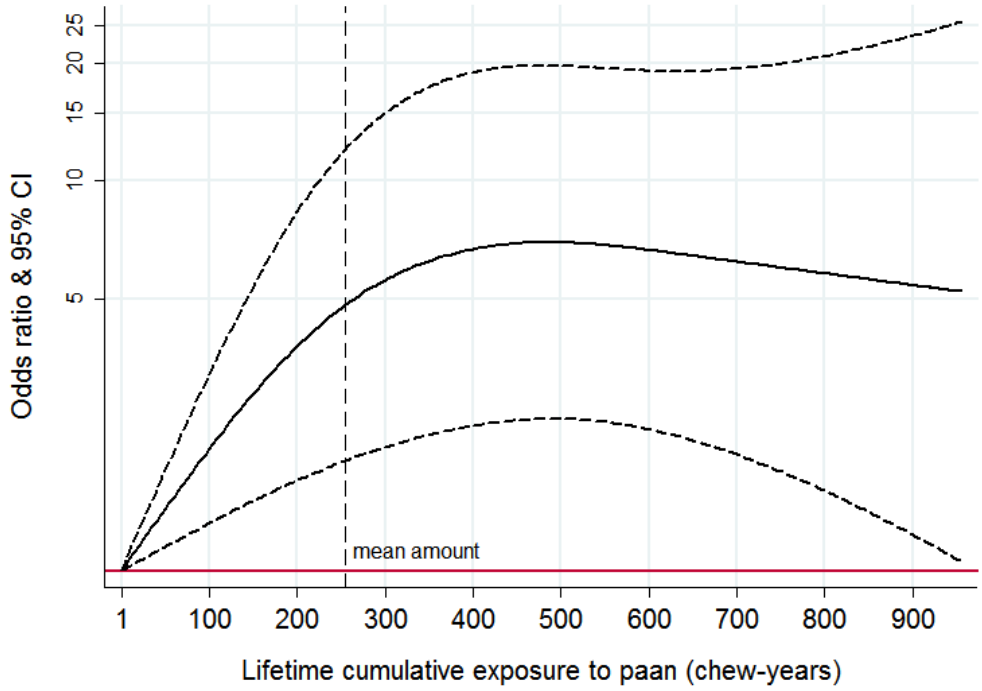
conservative in the selection of degree of smoothness in flexible models to reduce over-fitting of the curve to the data(224).

The lower AIC value of the 3 knot model compared to the linear model suggests a nonlinear dose-response curve. A likelihood ratio test was performed to test this hypothesis. The 3 knots model had a significantly improved fit compared to the linear model ($p = 0.023$), denoting a statistically significant deviation from linearity of the dose-response curve. The shape of the selected restricted cubic spline regression (3knots) model is presented in Figure 7-1. The solid line denotes the estimated ORs from the restricted cubic spline regression model and the dashed lines denote the approximate 95% pointwise confidence intervals. Since the continuous exposure variable was centered on its mean, only the shape of the curve and the relative values of ORs are important. The odds ratios could be interpreted as the effect of unit increase in chew-years among current chewers or, among past chewers who quit chewing paan 3 years before assessment (mean amount of quit-years), when all other confounders are held constant. The risk increased sharply up to the mean amount of chew-years (255.55) and increased more slightly until it reached the highest risk at 470 chew-years (OR = 6.96; 95%CI = 2.44 - 19.80). The risk did not increase after this point resulting in a plateauing of effect measure. Restricted cubic spline regression is known to be unstable at its tails, and sensitive to potential outliers, so the marginal reduction in risk with widening of confidence interval at high amounts of exposure (>600 chew-years) may not be interpretable(143,144).

Table 7-3: Akaike information criterion values for restricted cubic spline regression models of a dose-response relationship between paan chewing and risk of oral cancer

Number of knots	df	AIC values
Linear model	15	667.8545
3 knots	16	664.7158
4 knots	17	666.618
5 knots	18	664.2352
6 knots	19	664.1916
7 knots	20	665.8498

Figure 7-1: Nonlinear dose-response relationship between cumulative exposure to paan chewing (chew-years) and risk of oral cancer: restricted cubic spline regression with 3 knots*.



*adjusted for age, gender, smoking, alcohol consumption, lifetime material deprivation, number of missing teeth, years since cessation of paan and indicator variable for the paan chewing habit.

Years since quitting

Years since quitting was not significantly associated with oral cancer in any of the models tested. To find the cut-off point which defines a participant as a past chewer we tested different models with varying cut-off points (results not shown), but none of the models showed a significant association.

Discussion

Our study overcomes the shortcomings of traditional trend analysis by adopting a restricted cubic spline regression which is suggested in order to avoid erroneous linearity assumptions and power loss due to categorization. Unlike previous studies, we also took into account duration and frequency of paan chewing through the creation of a comprehensive summary variable – chew-years – additionally adjusting for years since cessation in the model.

Our results show a significant non-linear dose-response relationship between paan chewing and risk of oral cancer. The risk increases steeply at lower doses and attains a maximum level and plateaus thereafter.

Although it has been previously observed that a non-linear dose response exists in the association of alcohol consumption and cigarette smoking with oral cancer (147,148), this is the first epidemiological study reporting a nonlinear dose-response relation between paan chewing and oral cancer in an Indian population. Cohort studies on occupational exposures also have reported an attenuation of risk at high exposure levels(225–227). Some of the proposed explanations of this phenomenon are discussed below.

(i) Depletion of susceptible individuals in the population

Individuals who are genetically more susceptible to the exposure may succumb to death or disease and hence get depleted from the pool of the population at risk(228). Although this phenomenon may be highly exposure-specific, genetic susceptibility to paan has been reported(85) and could be one explanation of the observed nonlinearity of the dose-response relationship to paan.

(ii) High background rates of disease

There is a limit of how large the relative risk can be in a population based on the prevalence of the disease among the unexposed. Since prevalence of smoking, alcohol consumption and other competing risk factors are high in India, the background rate of oral cancer among never chewers of paan in India may be high. In our own study, 38 cancer cases (11.5%) had never been exposed to any of the three major oral cancer risk factors (paan, smoking or alcohol) and 91 cases

(27.5%) were never chewers of paan. Due high background rate of oral cancer in India and presence of several competing causes, one may not find a relative risk due to one single cause (paan chewing) beyond a certain value.

(iii) Measurement error

Misclassifications or mismeasurement of exposure may attenuate the estimated relative risk, however if the error depends on the true level of exposure, this bias could also be in the opposite direction(229). We adopted every possible measure to reduce measurement error with the use of the life grid technique and by recording complete history of the paan chewing habit in periods of the same frequency and type of product. Any change in the habit history was cross-referenced with other significant life events (e.g., marriage, change in job or house) that occurred approximately at the same time period to ensure the accuracy of recall. We believe these steps have considerably reduced the measurement error in our study.

(iv) Unaccounted confounding by other risk factors

Failure to address significant potential confounders in the analysis may lead to under- or overestimation. Moreover, the nature of influence of the unaccounted confounders may change the dose-response curve(228). For example, if the unaccounted risk factor is more prevalent among the low exposure group in the study the resultant dose-response curve may be attenuated at a high level of exposure of interest. In our study, potential confounders were selected based on a *priori* knowledge and unlike previous studies we have taken into account all major known risk factors for oral cancer pertaining to our population.

(v) Over measurement of cumulative exposure

In addition to the above mentioned six plausible explanations which have been show to attenuate the risk at high exposure levels, we also hypothesize that the measurement of biologically irrelevant levels of exposure could attenuate its effect when cumulative life time exposure is the exposure of interest. For diseases such as oral cancer with a long latency period and potential detectable precancerous stages, exposure measured after the biological initiation of the disease which went undetected will not be associated with risk. Late diagnosis of disease, unknown latency periods and individual variation in latency periods further complicate this issue.

Years since cessation

The years since cessation of paan were not significantly related to oral cancer in any of our models. Our results are in agreement with previous studies reported from India(29,74,138). A probable explanation of this result is the phenomenon of reverse causality: the participants who stopped chewing paan due to initial symptoms of the disease may not be affected by the years since cessation, because the disease had already initiated in the background. This has also been observed in lung cancer risk among recent quitters of smoking(186). Since the association was not statistically significant even in the unadjusted analysis we did not pursue the modeling of this effect any further (Table 7-1).

The carcinogenic potential of each ingredient of paan (tobacco, areca nut, betel leaf and slaked lime) may be different. However, we adopted a working definition of paan in our study, which is essentially any combination which has areca nut, smokeless tobacco or both. Hence, we were not able to estimate a dose-response relationship to different combinations or ingredients separately, which is one of the limitations of the study. However in Indian contexts, the same participant can use different combinations in different amounts at different points in their habit history and each of these changes in their habit may be interrelated. Although we did not have the information on the amount of each ingredient used in each combination by the participant, we believe that our method ensures maximum utilisation of the data in hand with an acceptable level of inaccuracy.

In addition to the relevance of a dose-response relation in establishing causality according to Hill's causality criteria, our results have wide public health implications.

In a population with high prevalence of paan chewing(23), it is important to know how the risk varies among people who have the habit rather than comparing them to non-chewers. Our study provides this quantitative estimation of risk among ever chewers of paan. Studies have shown that individual's perception of their own risk is often optimistically biased. This leads to a reduced motivation towards cessation of unhealthy behaviours, when coupled with the illusion of control over their own risk taking behaviours(230–232). A recent survey on health literacy associated with paan chewing in India reported 79% of the respondent knew that paan chewing is a potential risk factor for oral cancer(154), and 75% of ever paan chewers were aware that it could lead to cancer, yet they continue practicing it. From a clinician's standpoint our results could be used in motivational counselling for behaviour change (cessation of paan chewing) as a tool to avoid optimistic bias, and provide an opportunity to establish and discuss the realistic risk of the individual. Our results by interpolating a dose response curve rather than a basic trend in the risk, provide the clinician with an unique opportunity to discuss with the patient, their position in this curve and how continuing the habit could affect their risk.

Although numerous biochemical and animal studies have been conducted, the pathways of chemical carcinogenesis of paan chewing are not completely understood. Our results could be used in future epidemiological and biochemical studies which will help to better understand the biological processes behind the dose-dependent risk variations, which is an essential next step towards reducing oral cancer incidence associated with paan chewing, worldwide.

8. DISCUSSION

Specific public health implications of the results and discussion are provided at the end of each manuscript. The following section presents a broad perspective of this research project using the data from the HeNCe Life study –India site. Based on the study objectives, we restate the overall rationale of the project, followed by a summary of results from the two manuscripts. Strengths and limitations, as well as future research directions, are discussed thereafter.

8.1 Rationale

Oral cancer is widely distributed around the world with more than 2 million affected individuals. More than half of them are concentrated in Asia (55.3%), with India being a major contributor as shown by the age-standardized incidence rate of 7.5 oral cancer cases per 100,000individuals(14). India high incidence of oral cancer is attributed to the prevalent habit of paan chewing(23). Although the association between this secular cultural behaviour and oral cancer is well established, there are several dimensions of this habit that need further investigation.

Similar to other health related behaviours (e.g., smoking and alcohol consumption), the prevalence of paan chewing is high among children whose family members have the habit(106,107). However, most of the studies in this field have conceptual and analytical weaknesses such as they only reported simple descriptive statistics and did not took in to account potential confounders. In addition, only a few studies have investigated whether parents' and children's paan chewing habits are associated(108) and if yes, whether parent-child bonding modifies this association. It is known that children consider their parents and adults as role models and try to imitate them(190). When children observe their parents chewing paan, they may indirectly perceive the psychological and physiological rewards of the habit and this, coupled with children's natural tendency to imitate parents, could lead to initiation of habit. Such pathways of initiation would be stronger is societies which are interdependent such as India.

Hence, a better understanding of the connection between parents and children paan chewing habits may be of high importance in developing proactive interventions which may have long-lasting impacts.

The shape of the association between paan chewing and oral cancer risk is another aspect of this habit that needs to be better understood. Although the carcinogenicity of paan is well established and a positive dose-response trend has been proposed, most of the previous studies have adopted a linear trend analysis, which is known for its erroneous assumptions and power loss due to categorization(156). In addition, these studies only considered one dimension of the habit (duration or frequency), hence the results could be confounded due to the dimension unaccounted for. Alternative flexible modeling techniques, which are not based on the forced linearity assumption and raise no power loss concerns(140,156), have been proposed to overcome this limitation. However, only one study has investigated the dose-response between paan chewing oral cancer risk using a flexible modeling technique, but only considered the daily frequency of paan chewing. Also, it was carried out among the Taiwanese population where the use of betel quid without a tobacco is the common practice(222). In India, tobacco is often used as an ingredient in paan chewing(1). Understanding how risk changes depending on dose of exposure is important for a better understanding of background biological process leading to differential incidence of disease among exposed population.

In summary, it is essential to better understand these two important aspects – family influences on uptake of the habit and dose-response – of an individual's paan chewing for designing long-lasting and culturally sensitive prevention programs, individualistic risk assessment protocols which could be used in behaviour counselling, and development of cessation programs targeted towards high risk populations.

In this project, we investigate two aspect of paan chewing: associations between parents and children's habits and the dose-response relationship.

8.2 Summary of results

The following section is a brief summary highlighting the results from the two manuscripts included in this thesis work.

Manuscript I

The first manuscript in this thesis evaluated the association between the parental and the participant's paan chewing habit and the difference between maternal and paternal contribution in this association. We also investigated how this intergenerational transmission of the paan chewing habit, in South Indian families, is explained by the participants' perception of the relationship with their mothers and fathers.

Our findings showed that both the paternal and maternal paan chewing habits were significantly associated with the participant's paan chewing habit. Moreover, they were similar in effect size; both the paternal and maternal paan chewing habit increased the risk of the participant to start chewing paan, at some point in their lifetime, by approximately 3 times. Participants' perception of the relationship with their parents only marginally explained this association. However, maternal strictness was significantly associated with the participant's paan chewing habit.

To our knowledge none of the previous studies has investigated this intergenerational transmission in India. However, previous studies, mostly cross sectional surveys, have reported an increased prevalence of paan chewing habit among children of parents who had the habit(104,106,107). Along with peer influence, parental paan chewing has also been proposed as a determinant of initiation based on these survey results(93). By establishing the association and quantifying the maternal and paternal contributions, our results enrich the knowledge base which could serve as a platform for future studies and in designing interventions targeting parents and children.

Manuscript II

The objective of this manuscript was to estimate the dose-response relationship between the lifetime cumulative exposure to paan (chew-years) and risk of oral cancer using a flexible modeling technique. A secondary objective of this analysis was to investigate the association between years since cessation of paan chewing and risk of oral cancer.

Our results showed a significant non-linear dose-response relationship between lifetime cumulative exposure to paan (chew-years) and risk of oral cancer among ever chewers of paan. The adjusted odds ratio increased steeply with a unit increase in chew-years at low levels of exposure. However, no further increase in risk was observed after 470 chew-years resulting in a plateauing of risk at high exposure. Years since cessation of paan chewing was not significantly associated with risk of oral cancer, even with different cut-off points in the definition of past chewers.

A recent study from Taiwan has proposed a nonlinear dose-response relationship between paan chewing habit and oral cancer risk(222). However, this study only considered betel quid without tobacco, and the exposure of interest was limited to the daily consumption. Paan chewing habit is usually not a short term habit, and previous studies have noted a positive trend in dose response associated with duration of habit(85). To date, no studies have extensively investigated the shape of dose-response curve of paan chewing habit among India population.

Comprehensive and extensive measures of paan chewing habit history, strong methodological and analytical techniques add to the strength of our study.

8.3 Methodological considerations of present study

Results of a case-control study are considered as biased when the estimated odds ratio of the study differs from the true odds ratio observed in the source population due to systematic errors. Due to the systematic nature of these errors, increasing the sample size will not eliminate bias(233). Although complete elimination of bias is not possible, every possible measure should be taken to

reduce it. The following section will discuss such measures taken in our study to reduce the major types of biases.

8.3.1Selection bias

Selection bias occurs in case-control studies when the distribution of cases and controls is different from the source population(233). This difference in distribution could occur due to the following methodological errors.

8.3.1.1Selection bias due to different reference populations for cases and controls

The study base is the reference population from which the data for the study comes from(234). In a hospital based case-control study the cases and controls should be recruited from the same study base, otherwise bias can occur. In our study, there were two recruitment hospitals – the Government Dental College and the Government Medical College of Kozikode, they both are situated on the same campus, and serve the same reference population of Northern Kerala. Both of them are tertiary care centers based on a referral system and the services they provide do not overlap. Due to these facts, these two institutions could essentially be considered as one, and since controls were recruited from the same institutions as the cases they have probably gone through the same referral system to attend the hospitals. One of the eligibility criteria of the study was that the participant should be living within 150 kilometres from the site. This was an additional step to specify the study base.

8.3.1.2 Selection bias due to participation rate

Selection bias may occur when the recruited participants are not representative of the pool of eligible individuals in the study base. This could occur during the design phase when there is a substantial loss in enrolment of eligible participants (non-response) due to different reasons such as refusal by subject or severity of disease. In our study the participation rate among cases was 85.6% and among controls was 44.3%. These differential participation rates may have induced a certain amount of selection bias in our results.

If there is a systematic difference in exposure between those who were enrolled in the study and those who were not, this will result in biased estimates of true risk. Information on our main exposure (paan chewing) was not available for non-participating subjects. Therefore, we could not test whether they were systematically different from participating subjects. Nonetheless, non-participating subjects' demographic information was collected and although non-participating cases were older than participating cases, all other demographic variables were similarly distributed among the groups (see section 5.6.3). Although it is difficult to estimate the exact magnitude of bias, we could approximate the direction of bias as follows. Life time cumulative exposure to paan chewing habit is correlated with age and exposure status of the participant (current or past chewer). Given that the non-participant cases were older than participant cases; ever chewers of paan among them, most likely, would have had higher cumulative chew-years than participated cases. If this is true, our study may have under estimated the true dose-response, or in other words it is most likely that the direction of bias is towards the null.

8.3.1.3 Selection bias due to non-representative controls

Control participants in a case-control study should be a representative sample of the disease-free source population(157). Representativeness of our control subjects was explored by comparing data available from the Global Adult Tobacco (GATS) survey India 2009-2010(23). The proportion of current users of paan (10.2%) and never users of paan (82.5%) among our control group were very similar to the survey (10.7% and 86.5% respectively)(23). However, the proportion of past users of paan is marginally higher in our study (HeNCe Life – 7.3% and GATS – 2.8%).

In summary, we believe that although the non-participation rate was high in our control group, we were able to recruit a fairly representative sample of the source population with regards to the exposure of interest.

8.3.2 Information bias

Information bias occurs when cases and controls report exposure information differently due to several reasons. In our study the following measures were taken to reduce information bias.

The hypothesis of the study was not disclosed to the research assistants. These were trained rigorously in the data collection procedures and instructed to strictly follow the protocol. All three research assistants were well versed in the local language and culture, which is an essential component of questionnaire interviews as it initiates and maintains a good rapport with the participant. Cases were interviewed immediately after their histopathological diagnosis, which has been suggested to reduce information bias(233). Interviews were conducted in a hospital setting and with complete privacy, so that the participant was comfortable in sharing the information. For data collection, a structured questionnaire was used with the help of the life grid technique. The use of a life grid in retrospective data collection has shown to be effective in helping participants to recall information even after 50 years(165). Each new information collected during the interview was cross-referenced with major life events (e.g., marriage, birth of first child, first job) to ensure the temporal positioning and accuracy of information. Close to 10% of participants were re-interviewed after the original interview with a longer than 6 weeks' delay to assess the reliability of the data collection. This data is currently in the analysis stage and will be reported on soon.

8.3.3 Bias due to confounding

Potential confounders for all analyses were identified from a priori knowledge. For the association between parental and participant's paan chewing, directed acyclic graphs were created and the minimum set of confounders identified. These procedures increase the strength of our study by allowing us to appropriately take into account the confounding factors and to restrict residual confounding to a minimum(235).

8.3.4 Missing data

Even after applying rigorous methods to improve recall, participants were not able to recall certain information. Missing data was considered separately for each of the hypothesis tested in this project.

In the subset of data on which intergenerational transmission of PCH was investigated, the missing data was concentrated in two variables: maternal and paternal education, 16% of participants had missing value in either of the variables. The missing values in these two variables were imputed using multiple imputation by chained equation(179). Multiple imputation is one among the best practices proposed in such situations(176), to produce un biased results.

In the investigation of dose-response relationship less than 5% of subjects had missing value in lifetime material deprivation indicator. Since proportion of missing data was below 5%, listwise deletion was performed and analyses were done on complete observations, this procedure has shown to produce un biased estimates (236). Since the missing data were concentrated on confounders rather than exposures of interest, if left unattended would have resulted in biased estimate due to residual confounding. However, we adopted best available statistical technique to reduce the magnitude of this bias.

8.3.5 Generalizability

Results from hospital based case-control studies have lower generalizability compared to population based studies. In our study, every possible measure was adopted to reduce non-participation and thus increasing the sample size and representativeness. Although the participation rate among control subjects were low (Table 5-1), the prevalence of paan chewing habit (main exposure of interest) among those who participated were very similar to most recent available population based survey report on source population. Hence we believe that results of our study have sufficient generalizability.

8.4 Future research directions

Many decades of research support the aetiological role of paan chewing in causing oral premalignant and malignant lesions, yet the habit is highly popular in many parts of the world. Several studies have repeatedly established the association between paan chewing and oral cancer in different populations including India. However, recent studies report continuing high prevalence, low quitting rates of paan chewing (23,155), and a rising trend of oral cancer incidence among young individuals in India(237,238). These results should be taken as a sign to think beyond the simple objective of re-investigating the association between the habit and oral cancer, at least in India. There are many research areas which lay unexplored in the case of the paan chewing habit; intergenerational transmission and dose-response relation with oral cancer are only two of them.

With regards to the intergenerational continuity of paan chewing, more longitudinal and qualitative studies are needed to explore the complexities of this association.

More biochemical and molecular studies are needed to completely understand the complex biological process which leads to differential oral cancer incidence among those who are current and past chewers of paan. Measurement of behavioural exposure remains a challenge in observational studies. A widely practiced method is to assess exposure as an average of lifetime exposure. However, this is a highly subjective measure. Research is warranted to develop a comprehensive measure of lifetime exposure to paan and to solve the analytical challenges in considering different dimensions of exposure simultaneously.

The effect of quitting paan chewing on the risk of oral cancer is another less explored area. Although studies on premalignant conditions and lesions show that the risk is reduced after cessation of the habit, study results for oral cancer are contradictory. A better understanding of this relation may have widespread implications for public health policies.

Barriers to cessation of paan chewing also need to be better understood. Only 10% out of 42% of ever paan chewers who attempted to quit used cessation aids. Moreover, the use of cessation aids was negatively associated with successful attempts(155). Lack of health literacy may be one of the barriers. However, 79% of participants in a survey identified paan as cause of oral cancer and 75% of paan chewers were aware that their habit could lead to cancer(154). The authors identified the need for targeted health education and individualized risk assessment and counselling. More research is needed for developing such risk assessment protocols including establishment of the dose-dependent risk of an individual. To our knowledge, the results of our study are the first documentation of an intergenerational psychosocial transmission of paan chewing habit and nonlinear dose-response relationship between lifetime cumulative exposure to the habit and risk of oral cancer, in India. We believe that further research such as mentioned above would stem from our results in future.

8.5 Public health implications

Although objectives of manuscripts presented in this thesis work may seem to be theoretically unlinked, from a public health perspective it is of high importance to understand the two stages of paan chewing habit (intergenerational transmission and dose-response) among the same population. Two most important interventions against habits such as paan chewing are (i) increasing awareness among those who do not have the habit and thereby preventing them from acquiring it; (ii) motivating those who have the habit to refrain from it. Our study results contribute to both of these levels: prevention and cessation.

Based on the finding of significant association between parental and participant's PCH, targeted awareness programs and mass media campaigns could be developed taping on the morality of a responsible parent. Our results could also be used to identify high risk individuals through school based screening programs and intervene proactively. Moreover, our results signify the need for a family based intervention where collective effort of all the member of family is solicited for the eradication of the habit among them.

One of the pathways through which the intergenerational transmission occurs is through socialising behaviours of parents and the general norm for such behaviours in a culture. Our study results could also be used to motivate cultural and religious leader to become knowledge brokers to increase awareness among general population about the hidden harmful effects of such socializing behaviours which promote paan chewing.

In a population where the prevalence of paan chewing is high (more than one fourth of population are paan users in India (23)), it is equally important to act upon the practice of habit in addition to preventing its initiation. From the first-hand experience of the author of this thesis, one of the challenges faced by clinicians is to effectively communicate, in a limited time, the individualised risk patient has and to motivate them to refrain from habit based on their risk. However, the utilisation of the limited time available for behaviours counselling, is less effective due to the lack of an individualized risk assessment protocol. Currently there are no such protocols for assessing individualized risk for oral cancer due to paan chewing in India. Our results could be used as the platform from which future research could stem out and lead to development of such protocols. The carcinogenic pathways through which paan chewing leads to oral cancer are not completely understood. We believe that our study results of significant non-linear dose-response relationship will serve as stepping stone for future research to better understand the underlying biological processes.

9. CONCLUSION

The following conclusions could be drawn from the results presented in the two manuscripts comprised in the thesis.

- The paan chewing habit shows intergenerational continuity in South Indian families.

- In the intergenerational psychosocial transmission of the paan chewing habit mother's and father's habit play comparable roles.

- The parent-child relationship marginally explained the association between parental paan chewing and their offspring's paan chewing habit. Maternal strictness is positively associated with the paan chewing habit of the next generation.

- The dose-response relationship between lifetime cumulative exposure to paan chewing and risk of oral cancer is significantly non-linear. The risk increased steeply at lower levels of cumulative chew-years before reaching a plateau at high exposure.

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11. APPENDIX I

Consent forms (English & Malayalam)

A LIFE COURSE APPROACH TO THE AETIOLOGY OF HEAD AND NECK CANCER: HeNCe LIFE STUDY

Dr Ipe Varghese
Government Dental College

Purpose of the study

Previous studies have shown that certain adult chronic diseases such as cancer and heart disease may be influenced by social and psychological circumstances during birth, childhood, adolescence and early adult life. It is suggested that the build-up of problematic circumstances throughout life is the cause of disease rather than circumstances that happen at one point in time. Based on this idea, we are conducting a study to clarify if certain conditions and habits that people experience at different periods of their life are related to cancer of the mouth and/or throat. We want to know, for example, if people who experienced physical and/or chemical hazards at work will be more likely to have cancer in their mouth and/or throat; if people who had fewer educational opportunities were more likely to start behaviours such as smoking and alcohol drinking, and how these behaviours in turn, would affect their chances of having cancer in the mouth and throat.

Description of the research

The study will compare people who have mouth and/or throat cancer (Group 1) to people who do not have this disease (Group 2). It will take place in the Government Dental College in Calicut-India. A total of 800 people, 400 with cancer of the mouth or throat and 400 without will be invited to participate in this project. The research will be conducted in two parts and it will follow the same steps for both groups.

In the first part we are going to collect information from the medical records. For people in group 1, for example, we want to know medical details about the cancer. For people in group 2, we need to collect information on the reason for being in seen at the hospital, at which clinic they are consulting, etc.

The second part of the study will be an interview. In this second phase, we are going to use a questionnaire to ask people more detailed information about different aspects of their life such as work, housing conditions and family life. This part of the interview will take about 2 hours.

If I participate in this study, what will be involved?

Participating in this study means that you will allow us to look at your hospital medical records and that you will attend an appointment to carry out a two hour interview.

Potential harms, injuries, discomforts or inconveniences

There is no risk associated with participating in this study. It involves no treatment or procedures that can cause harm, injuries or discomfort. It involves only collection of data by means of an interview and medical files.

Potential benefits

Participants will not benefit directly from their participation in this study. However, the results from this study may contribute to the understanding of the development of head and neck cancers.

Participation

Participation in this research project is entirely voluntary.

Will participation in this study affect my treatment?

Participating will in no way affect your treatment or your medical follow-up.

What happens if I want to withdraw from this study?

You are perfectly free to withdraw from this research project at any time you want to – even in the middle of the interview. Such withdrawal will in no way affect your medical follow-up or treatment.

Confidentiality

We assure that all information gathered during the course of this research project will be kept completely confidential. Only the researchers involved in this project and the research assistants gathering the data will have access to the information you provide, which will be kept locked in the research office. All the data will be identified through a code number so we will not know to whom the data are related. The results of the research will be published in scientific journals in an anonymous form. All the data will be kept for a period of 5 years after which they will be destroyed.

Further information

If you would like any more information or have any questions related to this study, please do not hesitate to contact the project leader, Shameena ***phone number***.

Consent

I have read the information above, asked questions and received answers concerning areas that were unclear and I willingly agree to participate in this study. My participation is completely voluntary. I may withdraw at any time without it affecting my medical follow-up or treatment. I will not have waived any of my legal rights by signing this consent form. Upon signing this form, I will receive a copy of the entire consent.

_____

Participants Name

_____Date _____

Participants Signature

_____

Witness/. Name

_____Date_____

Witness/ signature

_____

Name of the person who explained the consent form.

_____ _____

Signature of the person who explained the consent form *Date*

തലയെയും കഴുത്തിനെയും ബാധിക്കുന്ന അർബുദത്തിന്റെ കാരണങ്ങളെക്കുറിച്ചുള്ള സമഗ്രപഠനം

ഡോ ഐപ്പ് വർഗീസ്
ഗവ. ഡെന്റൽ കോളേജ്

പഠനലക്ഷ്യം

മുൻകാലപഠനങ്ങൾ കാണിക്കുന്നത് ഒരു വ്യക്തിയുടെ ജനനം കുട്ടിക്കാലം, യൗവനം തുടങ്ങിയ കാലഘട്ടങ്ങളിലെ മാനസിക സാമൂഹിക സാഹചര്യങ്ങൾ അർബുദം, ഹൃദയസംബന്ധമായ അസുഖങ്ങൾ എന്നിവയെ സ്വാധീനിക്കുന്നു എന്നാണ്. ജീവിതകാലം മുഴുവൻ നീ□ ുനിൽക്കുന്ന പ്രശ്നകരമായ സാഹചര്യങ്ങളാണ് പെട്ടെന്ന് ഒരു ദിവസം ഉ□ ാകുന്ന കാരണങ്ങളേക്കാൾ അസുഖത്തിന് കാരണമാകുന്നത്. ആയതിനാൽ ജനങ്ങൾ ജീവിതത്തിന്റെ ഓരോ ഘട്ടങ്ങളിൽ തുടങ്ങിവെക്കുന്ന ശീലങ്ങൾ വായിലേയും തൊ□ യിലേയും അർബുദവുമായി എങ്ങിനെ ബന്ധപ്പെട്ടിരിക്കുന്നു എന്നറിയുവാനാണ് ഈ പഠനം നടത്തുന്നത്. ഉദാഹരണത്തിന് രാസവസ്തുക്കൾ മൂലമോ മോശം ഭൗതികസാഹചര്യം മൂലമോ ആപത്കരമായി ജോലി ചെയ്യേ□ ി വരുന്ന ആളുകൾക്കാണ് വായിലും തൊ□ യിലും അർബുദം വരാനുള്ള സാധ്യത. അല്ലെങ്കിൽ വിദ്യാഭ്യാസപരമായി പിന്നോക്കം നിൽക്കുന്നവരിൽ പുകവലി, മദ്യപാനം മുതലായ ദുഃശീലങ്ങൾ വർദ്ധിക്കുന്നതും അത് വായിലെ അർബുദവുമായി എങ്ങനെ ബന്ധപ്പെട്ടിരിക്കുന്നു എന്നതിനെ സംബന്ധിച്ച്.

ഗവേഷണത്തെക്കുറിച്ചുള്ള വിവരണം

ഈ ഗവേഷണത്തിൽ ആളുകളെ ര□ ുവിഭാഗമായി തിരിച്ചിരിക്കുന്നു. (ഒന്നാം സംഘം) വായിലും തൊ□ യിലും അർബുദം ഉള്ളവർ. (ര□ ാം സംഘം) അസുഖം ഇല്ലാത്തവർ. ഈ ഗവേഷണം കോഴിക്കോട് ഗവൺമെന്റ് ഡെന്റൽ കോളേജിൽ വച്ച് നടക്കുന്നു. ആകെ 800 ആളുകൾ. അവർ 400 പേർ അസുഖമുള്ളവർ, ബാക്കി നാനൂറ് പേർ അസുഖം ഇല്ലാത്തവർ. ഗവേഷണം ര□ ുഘട്ടങ്ങളായാണ് നടക്കുക. ര□ ു വിഭാഗക്കാരിലും ഒരേ പഠന നടപടികളാണ് കൈകൊള്ളുക.

1. ആദ്യഘട്ടത്തിൽ വിവരങ്ങൾ ആശുപത്രിരേഖകളിൽ നിന്നും ശേഖരിക്കുന്നു. ഉദാഹരണത്തിന് ഒന്നാം വിഭാഗക്കാരായ ആളുകളുടെ അസുഖസംബന്ധിയായ വിശദാംശംങ്ങൾ അന്വേഷിക്കും, ര□ ാംവിഭാഗക്കാരായവർ ആശുപത്രികളിൽ പോകുവാനു□ ായ സാഹചര്യങ്ങളെക്കുറിച്ച് തിരക്കും.

2. പഠനത്തിന്റെ ര□ ാംഘട്ടം അഭിമുഖമാണ്. ചോദ്യാവലിയുടെ സഹായത്തോടെ, തൊഴിൽ, ജീവിതസാഹചര്യങ്ങൾ തുടങ്ങി ജീവിതത്തിന്റെ വിവിധ തുറകളെക്കുറിച്ചുള്ള സൂക്ഷ്മ വിവരം ലഭ്യമാക്കുന്നു. അഭിമുഖത്തിന്റെ ദൈർഘ്യം ര□ ു മണിക്കൂർ ആണ്.

ഞാൻ ഈ പഠനത്തിൽ പങ്കുചേർന്നാൽ എങ്ങനെ അതുമായി ബന്ധപ്പെട്ടിരിക്കും

ഈ പഠനത്തിൽ പങ്കെടുക്കുക എന്നുവെച്ചാൽ നമ്മുടെ ആശുപത്രി രേഖകൾ പരിശോധിക്കുവാൻ അനുവദിക്കുക എന്നും അഭിമുഖത്തിൽ പങ്കെടുക്കുക എന്നും ആണ്.

പഠനവുമായി ബന്ധപ്പെട്ട് എന്തെങ്കിലും അപകടരമായ സാഹചര്യങ്ങളോ, അസൗകര്യങ്ങളോ നിലനിൽക്കുന്നു□ ാ ?

ഈ പഠനവുമായി ബന്ധപ്പെട്ട് യാതൊരു അപകടവും നിലനിൽക്കുന്നില്ല. അപകടമോ, അസ്വസ്ഥതയോ ഉളവാക്കുന്ന ഒരു ചികിത്സാരീതിയും ഇതിൽ ഇല്ല. ആശുപത്രിരേഖകളും അഭിമുഖവും വഴി വിവരങ്ങൾ ശേഖരിക്കുക മാത്രമെ ചെയ്യുന്നുള്ളു.

പഠനവുമായി ബന്ധപ്പെട്ട് എനിക്ക് എന്തെങ്കിലും മെച്ചം ലഭിക്കുമോ ?

പങ്കെടുക്കുന്നവർക്ക് നേരിട്ട് യാതൊരു മെച്ചവും ലഭിക്കുന്നതല്ല. എങ്കിലും ഈ പഠനത്തിന്റെ ഫലം വായിലേയും, തൊ□ യിലേയും അർബുദസംബന്ധമായി കൂടുതൽ വിവരങ്ങൾ നമുക്ക് പ്രദാനം ചെയ്യുമെന്ന് പ്രത്യാശിക്കാം.

പഠനത്തിൽ പങ്കെടുക്കുന്നത് സംബന്ധിച്ച്

ഈ പഠനപദ്ധതിയിൽ പങ്കെടുക്കേ□ ത് സ്വമേധയാ ആണ്

ഈ ഗവേഷണത്തിൽ പങ്കെടുക്കുന്നത് എന്റെ ചികിത്സയെ ബാധിക്കുമോ ?

ചികിത്സയേയോ ചികിത്സാനന്തരനടപടികളെയും പഠനം യാതൊരു കാരണവശാലും ബാധിക്കുന്നതല്ല.

ഈ പഠനത്തിൽ നിന്ന് പിൻവാങ്ങണമെന്ന് കരുതിയാൽ അതിന്റെ അനന്തരഫലങ്ങൾ എന്തായിരിക്കും ?

ഈ ഗവേഷണപദ്ധതിയിൽ നിന്ന് ഏതു സമയത്തും അതായത് അഭിമുഖത്തിന്റെ പകുതിയിൽ വെച്ച് പോലും പിൻമാറാനുള്ള പൂർണ്ണ അവകാശം നിങ്ങൾക്കു□ ്. അത് നിങ്ങളുടെ ചികിത്സയെ ഒരു കാരണവശാലും ബാധിക്കുന്നതല്ല.

പഠനത്തിന്റെ വിശ്വസ്തത

ഗവേഷണവേളയിൽ നിങ്ങൾ നൽകുന്ന വിവരങ്ങൾ പൂർണ്ണരഹസ്യസ്വഭാവത്തോടെ സൂക്ഷിക്കുന്നതായിരിക്കും എന്ന് ഉറപ്പ് തരുന്നു. നിങ്ങൾ നൽകിയ വിവരങ്ങളുമ ായി ഗവേഷകർക്കും, വിവരം ശേഖരിക്കുന്ന ഗവേഷകസഹായികൾക്കുമല്ലാതെ മറ്റാർക്കും പ്രാപ്യത ഉ□ ായിരിക്കുന്നതല്ല. പ്രസ്തുത വിവരങ്ങൾ ഗവേഷണകാര്യാലയത്തിൽ ഭദ്രമായി പൂട്ടി

സൂക്ഷിക്കുന്നതാണ്. കൂടാതെ നിങ്ങൾ നൽകുന്ന വിവരങ്ങൾ ഒരു രഹസ്യ അക്കം ഉപയോഗിച്ച് ഏകോപിപ്പിക്കുന്നതിനാൽ അവയെ വ്യക്തിപരമായി ആരുടേതെന്ന് തിരിച്ചറിയാൻ സാധ്യമല്ല. ഗവേഷണഫലം ശാസ്ത്രമാസികകളിൽ പ്രസിദ്ധീകരണത്തിന് നൽകുമ്പോൾ വ്യക്തിപരമായി തിരിച്ചറിയാത്ത രീതിയിലാണ് നൽകുക. ഗവേഷണസംബന്ധമായ എല്ലാ വിവരങ്ങളും 5 വർഷത്തേക്ക് സൂക്ഷിച്ച് വെക്കുകയും അതിന് ശേഷം നശിപ്പിച്ചു കളയുകയും ചെയ്യുന്നതാണ്.

കൂടുതൽ വിവരങ്ങൾക്ക്

പഠനവുമായി ബന്ധപ്പെട്ടുള്ള നിങ്ങളുടെ സംശയങ്ങൾക്കും ആശങ്കകൾക്കും വിവരങ്ങൾക്കും വേ□ ി തലവൻ ഡോക്ടർ ഷമീനയുമായി ബന്ധപ്പെടുക.
ഫോൺ:.....

സമ്മതം

ഞാൻ മുകളിൽ കൊടുത്തിരിക്കുന്ന വിവരങ്ങൾ വായിക്കുകയും സംശയനിവാരണം നടത്തുകയും സ്വമനസ്സാലെ ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതം രേഖപ്പെടുത്തുകയും
ചെയ്തിരിക്കുന്നു. സ്വമനസ്സാലെയാണ് ഞാൻ ഇതിന് സമ്മതിച്ചിരിക്കുന്നത്. ഞാൻ എന്റെ ചികിത്സയെ ബാധിക്കാത്ത വിധം എപ്പോൾ വേണമെങ്കിലും ഈ പഠനത്തിൽ നിന്ന് പിൻവലിയുന്നതാണ്. ഈ സമ്മതപത്രം ഒപ്പിടുന്നതു വഴി ഞാൻ എന്റെ ഒരു നിയമപരമായ അവകാശവും ബലികഴിച്ചിട്ടില്ല. ഇത് ഒപ്പിടുന്നത് വഴി സമ്മതപത്രത്തിന്റെ ഒരു പകർപ്പ് എനിക്ക് ലഭിക്കുന്നതാണ്.

പങ്കെടുക്കുന്നയാളുടെ പേര് തിയ്യതി

പങ്കെടുക്കുന്നയാളുടെ ഒപ്പ് തിയ്യതി

സാക്ഷി പേര് തിയ്യതി

സാക്ഷി ഒപ്പ് തിയ്യതി

റിസർച്ച് അസിസ്റ്റൻറ് പേര് തിയ്യതി

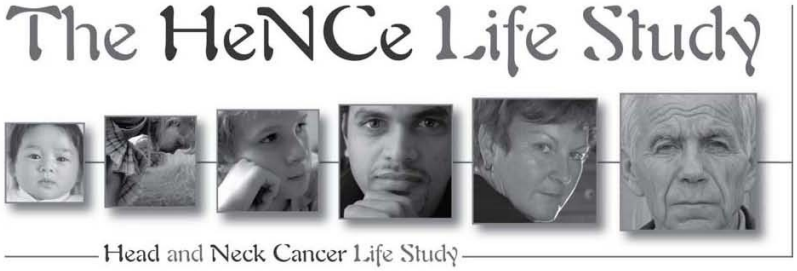
റിസർച്ച് അസിസ്റ്റൻറ് ഒപ്പ് തിയ്യതി

12. APPENDIX II

Questionnaire (Back translated to English)

CONFIDENTIAL

MULTI CENTER STUDY OF HEAD AND NECK CANCER:
HeNCe Life Study



UNIT OF EPIDEMIOLOGY & BIOSTATISTICS
INRS-INSTITUT ARMAND FRAPPIER – LAVAL – CANADA

FACULTY OF DENTISTRY & DEPARTMENT OF EPIDEMIOLOGY
MCGILL UNIVERSITY – MONTREAL - CANADA

HOSPITAL DO CÂNCER-DEPARTAMENTO DE CIRURGIA DE CABEÇA E PESCOÇO - SÃO PAULO-BRASIL

SCHOOL OF DENTISTRY - FACULTY OF HEALTH SCIENCES
UNIVERSITY OF LIMPOPO - MEDUNSA - SOUTH AFRICA

GOVERNMENT DENTAL COLLEGE –MEDICAL COLLEGE CAMPUS
KOZHIKODE – SOUTH INDIA

2008

Medical information | 0 5 Country | ID N°

TABLE OF CONTENTS

Medical information | 0 5 Country | ID N°

A. MEDICAL INFORMATION

Interviewer Reminder: Prior to interview, obtain information below from research file or medical records.

Identification Number..... 0 5 - **Country** **Participant**

Country: (01) Brazil (02) Canada (03) South Africa (04) United Kingdom (05) India

A1 Status: .....
(01) Case (02) Control

A2 Subject's Initials (Surname, Name) .....

A3 Hospital / Recruitment site.....
(01) Governmental Dental College (02) Governmental Medical College

FOR CONTROLS :

A4 Control Department: *(Code 88 for cases)*.....
(01) Dermatology (05) Gynecology
(02) Dental Clinic (06) Opthalmology
(03) Ear, Nose and Throat (07) Orthopedics
(04) Gastroenterology (08) Nephrology

A5 Main Diagnosis of CONTROL in this department (LC)..... -
Condition description: _____

FOR CASES:

A6 Cancer site: .....
(01) Tongue (02) Floor of mouth (05) Others specify……
(03) Gum (04) Buccal mucosa

A7 Global TNM stage T_____ N_____ M____ ➔ Global Staging **(LC)** _____

A8 Date of Diagnosis..... - - -
(99-99-9999) Don't know Day Month Year

A9 Time since Diagnosis (months).....

A10 Interviewer's Initials (Surname, Name).....

A11 *Interviewer:* **Was a proxy used?**
(01) Yes (02) No

3

Section B – General Information | 0 5 Country | ID N°

B. GENERAL INFORMATION

B1 Date of Interview..... Day - Month - Year

B2 Time of beginning of Interview..... **Hour** - **Minute**

B3 Interview .....
(01) Original (02) Duplicate *(6-12 weeks later)* (3) Duplicate *(+12 weeks later)*

B4 Sex.....
(01) Female (02) Male

Interviewer Reminder: Present life grid here. See instructions in guidebook.

B5 What is your date of birth?..... Day - Month - Year
(99-99-9999) Don't know

B6 How old are you?.....

B7 Do you live in a rural (farm) or urban (in a city) area? .....
(01) Urban (02) Rural (GO TO B9)

B8 If you live in an urban area, what city do you live in? (LC).....
Name of City: _____

Interviewer Reminder: Confirm name of city from list of codes.Rural area is in the farm

B9 How many years have you been living there? (Last consecutive years).....
(00) Less than one year (GO TO B10)

B10 Were you born in a rural (farm) or an urban (in a city) area?.....
(01) Urban (02) Rural (GO TO B12)

B11 If you were born in an urban area, what city were you born in? (LC) .....
Name of city: _____
(00) Other country

B12 How many years did you live there?.....
(00) Less than one year

Section B – General Information | 0 5 Country | ID N°

B13 What is your religion? (Show Answer Sheet).....

(00) None (GO TO B16)
(01) Hindu
(02) Muslim
(03) Christian
(04) Sikh
(05) Buddhist/Neo-Buddhist
(06) Jain
(07) Jewish
(08) Parsi/ Zoroastrian
(09) Other, specify_____.....

B14 Do you practice this religion?.....

(00) No (GO TO B18)
(01) Yes

B15 How old were you when you started practicing this religion?.....

(00) My whole life

B16 What is the cast or tribe of you belong to?

Caste:_____ Tribe: _____

(00) No Cast/Tribe
(99) Don`t know / Prefer not to say

B17 What type of caste / tribe is this?.....

(01) Forward caste
(02) Backward caste
(03) Other backward caste (OBC)
(04) Scheduled caste
(05) Scheduled tribe
(06) None of them
(99) NA/ Christian

5

Section C – Education | 0 5 Country | ID N°

C. EDUCATION

This section is about your education. Firstly,

C1 Did you ever attend school?.....
(01) Yes (GO TO C3)
(02) No, school was too far away
(03) No, transport was not available
(04) No, education was not considered necessary
(05) No, I was required for household work/ farm work/ family business
(06) No, I was required for outside work for payment in cash or kind
(07) No, school costed too much
(08) No, there were no proper school facilities for girls
(09) No, other reason for not attending, specify:_____

C2 Can you read and write?.....
(00) No (GO TO SECTION D)
(01) Yes (GO TO SECTION D)
(02) Yes, I learned with Saksharatha

Interviewer Reminder: Collect general information using the **life grid**
- Situate years of **formal** education i.e. that were successfully completed at school.

C3 How many years of formal education do you have? .....

C4 What was the highest standard that you obtained?.....
(01) Lower Primary (1-4 yrs)
(03) Upper Primary (5-7 yrs)
(04) High School (8-10 yrs)
(05) PDC (11-12)
(06) University
(07) Post-graduate
(07) Technical certificate

C5 Have you ever failed a school year?.....
(00) No
(01) Yes, once
(02) Yes, twice
(03) Yes, 3 or more times

Section D – Occupations & Employment | 0 5 Country | ID N°

D. OCCUPATIONS & EMPLOYMENT

In this section I would like to ask you a few questions about jobs you may have had.

Interviewer Reminder:. A job is a **continuous period of time of ONE YEAR OR MORE working and paid by the same employer** even though the participant may have had different positions during that period. If the participant was self-employed, a job is considered to be a period of time doing the same type of self-employed work.

D1 Have you ever had a paid job in your life (> 1 year)?..... ☐☐
(00) No (GO TO SECTION E) (01) Yes
(02) No, I was a housewife (ANSWER D13-D27)

D2 Which of the options below best describes your work situation in the past 7 days?..... ☐☐
(01) Full time work (30+ hours/ week) (05) Permanently sick or disabled
(02) Part time work (< 30 hours/ week) (06) On sick leave
(03) Unemployed (07) Other (Specify:_____)….. ☐☐
(04) Fully retired from work

Let's look at the different jobs you've had, the different positions you may have held. Again, we will use this grid to help us out and refer to it for the specific questions I will have afterwards.

D3 Since you started working how many jobs have you had?..... ☐☐
(01) (02) (03) (04) (05) (06) (07) (08) (09 or more)

Section D – Occupations & Employment | 0 5 Country | ID N°

FIRST JOB

Interviewer Reminder: Confirm which job is 1st job with life grid.

I would like to ask you a few questions about your **first job**. So,

D4 You were doing that job...

From age?	To age?	# Years	# Months
			8 8

D5 Did you occupy different positions at that job?.....
(00) No (Fill in FIRST column only) (01) Yes

	FIRST	LAST
D6 Please describe your job / different positions (LC).....		

FIRST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

LAST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

D7 What did the company you worked for specialise in?(LC).....
_____
_____

D8 Were you an employee or self-employed?……..
(01) Employee (02) Self-employed (GO TO D10)

8

Section D – Occupations & Employment | 0 5 Country | ID N°

D9 As an EMPLOYEE, which of the following best suited your position?.....
(00) I did not supervise anyone (02) Manager: Firm of <25 employees
(01) Foreman, supervisor, team leader (03) Manager: Firm of >25 employees

D10 If SELF-EMPLOYED, which of the following best suited your position?.....
(00) Without business (03) With <25 employees
(02) With business but without employees other than family members (04) With >25 employees
(05) Professional

D11 How many hours a week?.....

D12 How much were you paid PER YEAR at that time?
Describe: _____

- Calculate average amount in thousands of Indian Rupees
- Average: hourly rate x 35 hours x 50 weeks OR Min + Max / # yrs, prorated
- Self-employed: average earnings per year as per income tax declarations if submitted

Now I would like to ask you a few questions about work environmental hazards. Consider your job in general, regardless of the different positions you may have occupied.

Did your work often expose you to...?

D13 Dust.....
For example: Coal dust, metal dust, insulation material dust, wood dust, grain dust, textile fibers, plastic fibers, silica dust, saw dust, sanding dust, epoxy-resins, welding...)
(00) No (01) Yes

D14 Oils (Mineral oils, lubricating oils, cutting oils).....
(00) No (01)Yes

D15 Solvents (ex. Degreasing agents, cleaning agents, paint or lacquer removers or thinners).....
(00) No (01)Yes

D16 Acids or alkalis.....

(00) No (01) Yes

D17 Smoke (e.g., Engine emissions from diesel, gas or propane engines, or gases from coal, wood, rubber...).....
(00) No (01) Yes

Section D – Occupations & Employment | 0 5 Country | ID N°

D18 Gas (e.g. Combustion gases from industrial ovens, oxygen, ammonia...) or Fumes (ex. Metal fumes.....
(00) No (01) Yes

D19 Fumes (e.g., Metal fumes).....
(00) No (01) Yes

D20 Pesticides (e.g., insecticides, herbicides, fungicides or wood preservatives)
(00) No (01) Yes

D21 Did your work involve working with substances such as: Bethune, asphalt, alcohol, gasoline, glue, mercury, kerosene, dyes, inks etc? .....
(00) No (01) Yes

D22 Cigarette smoke……..
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

D23 Did your work <u>often</u> involve exposure to other chemicals?.....
(00) No (01) Yes, specify: _____.....

D24 Electromagnetic radiations (x-rays, microwaves, radioactive substances)?
(00) No (01) Yes

D25 Did you use any kind of protection for chemical / physical hazards (ex. masks, gloves)?.....
(00) No (02) Yes, sometimes
(01) Yes, most of the time (03) Yes, rarely

D26 Was your first job the same one as your longest job?....
(00) No (01) Yes, the same one as my longest job (GO TO D50)
(02) Yes, the same one my whole life (GO TO SECTION E)
(03) Yes, I was a housewife my whole life (GO TO SECTION E)

Section D – Occupations & Employment | 0 5 Country | ID N°

LONGEST JOB

Now I would like to ask you some questions about your **longest job**. I will be using the same set of questions I used in the previous section. So,

Interviewer Reminder: Confirm which job is longest job with life grid.

D27 You were doing that job...

From age?	To age?	# Years	# Months
			8 8

D28 Did you occupy different positions at that job?.....
(00) No (Fill in FIRST column only) (01) Yes

	FIRST	LAST
D29 Please describe your job / different positions (LC).....		

FIRST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

LAST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

D30 What did the company you worked for specialise in?(LC).....
_____
_____

D31 Were you an employee or self-employed?.....
(01) Employee (02) Self-employed (GO TO D33)

Section D – Occupations & Employment | 0 5 Country | ID N°

D32 As an EMPLOYEE, which of the following best suited your position?.....
(00) I did not supervise anyone (02) Manager: Firm of <25 employees
(01) Foreman, supervisor, team leader (03) Manager: Firm of >25 employees

D33 If SELF-EMPLOYED, which of the following best suited your position?.....
(00) Without business (03) With <25 employees
(02) With business but without employees other than family members (04) With >25 employees
(05) Professional

D34 How many hours a week?.....

D35 How much were you paid PER YEAR at that time?
Describe: _____

- Calculate average amount in thousands of Indian Rupees
- Average: hourly rate x 35 hours x 50 weeks OR Min + Max / # yrs, prorated
- Self-employed: average earnings per year as per income tax declarations if submitted

Now I would like to ask you a few questions about work environmental hazards. Consider your job in general, regardless of the different positions you may have occupied.

Did your work expose you to...?

D36 Dust .....
For example: Coal dust, metal dust, insulation material dust, wood dust, grain dust, textile fibers, plastic fibers, silica dust, saw dust, sanding dust, epoxy-resins, welding...)
(00) No (01) Yes

D37 Oils (Mineral oils, lubricating oils, cutting oils).....
(00) No (01)Yes

D38 Solvents (ex. Degreasing agents, cleaning agents, paint or lacquer removers or thinners).....
(00) No (01)Yes

D39 Acids or alkalis.....
(00) No (01) Yes

D40 Smoke (ex. Engine emissions from diesel, gas or propane engines, or gases from coal, wood, rubber...).....
(00) No (01) Yes

Section D – Occupations & Employment | 0 5 Country | ID N°

D41 Gas (ex. Combustion gases from industrial ovens, oxygen, ammonia...) or Fumes (ex. Metal fumes.....
(00) No (01) Yes

D42 Fumes (ex. Metal fumes).....
(00) No (01) Yes

D43 Pesticides (ex. insecticides, herbicides, fungicides or wood preservatives)
(00) No (01) Yes

D44 Did your work involve working with substances such as: Bethune, asphalt, alcohol, gasoline, glue, mercury, kerosene, dyes, inks etc? .....
(00) No (01) Yes

D45 Cigarette smoke……..
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

D46 Did your work <u>often</u> involve exposure to other chemicals?.....
(00) No (01) Yes, specify: _____.....

D47 Electromagnetic radiations (x-rays, microwaves, radioactive substances)?
(00) No (01) Yes

D48 Did you use any kind of protection for chemical / physical hazards (ex. masks, gloves)?.....
(00) No (02) Yes, sometimes
(01) Yes, most of the time (03) Yes, rarely

D49 Was your longest job the same one as your latest/ or current job?.....
(00) No
(01) Yes, the same one as my latest/current job (GO TO SECTION E)

Section D – Occupations & Employment | **0 5** Country | ID N°

LAST/LATEST JOB

Finally about your last/latest job...

Interviewer Reminder: Confirm which job is last/latest job with life grid.

D50 You were doing that job...

From age?	To age?	# Years	# Months
			8 8

D51 Did you occupy different positions at that job?.....
(00) No (Fill in FIRST column only) (01) Yes

	FIRST	LAST
D52 Please describe your job / different positions (LC).....		

FIRST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

LAST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

D53 What did the company you worked for specialise in?(LC).....
_____
_____

D54 Were you an employee or self-employed?.....
(01) Employee (02) Self-employed (GO TO D56)

D55 As an EMPLOYEE, which of the following best suited your position?.....
(00) I did not supervise anyone (02) Manager: Firm of <25 employees
(01) Foreman, supervisor, team leader (03) Manager: Firm of >25 employees

Section D – Occupations & Employment | Country: 0 5 | ID N°: ___

D56 If self-employed, which of the following best suited your position?.....

(00) Without business
(02) With business but without employees other than family members
(03) With <25 employees
(04) With >25 employees
(05) Professional

D57 How many hours a week?.....

D58 How much were you paid PER YEAR at that time?

Describe: _____

- Calculate average amount in thousands of Indian Rupees
- Average: hourly rate x 35 hours x 50 weeks OR Min + Max / # yrs, prorated
- Self-employed: average earnings per year as per income tax declarations if submitted

Now I would like to ask you a few questions about work environmental hazards. Consider your job in general, regardless of the different positions you may have occupied.

Did your work often expose you to...?

D59 Dust.....
For example: Coal dust, metal dust, insulation material dust, wood dust, grain dust, textile fibers, plastic fibers, silica dust, saw dust, sanding dust, epoxy-resins, welding...)
(00) No (01) Yes

D60 Oils (Mineral oils, lubricating oils, cutting oils).....
(00) No (01)Yes

D61 Solvents (ex. Degreasing agents, cleaning agents, paint or lacquer removers or thinners).....
(00) No (01)Yes

D62 Acids or alkalis.....
(00) No (01) Yes

D63 Smoke (ex. Engine emissions from diesel, gas or propane engines, or gases from coal, wood, rubber...).....
(00) No (01) Yes

D64 Gas (ex. Combustion gases from industrial ovens, oxygen, ammonia...) or Fumes (ex. Metal fumes.....
(00) No (01) Yes

Section D – Occupations & Employment | 0 5 Country | ID N°

D65 Fumes (ex. Metal fumes).....
(00) No (01) Yes

D66 Pesticides (ex. insecticides, herbicides, fungicides or wood preservatives)
(00) No (01) Yes

D67 Did your work involve working with substances such as: Bethune, asphalt, alcohol, gasoline, glue, mercury, kerosene, dyes, inks etc? .....
(00) No (01) Yes

D68 Cigarette smoke……..
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

D69 Did your work <u>often</u> involve exposure to other chemicals?.....
(00) No (01) Yes, specify: _____.....

D70 Electromagnetic radiations (x-rays, microwaves, radioactive substances)?.....
(00) No (01) Yes

D71 Did you use any kind of protection for chemical / physical hazards (ex. masks, gloves)?.....
(00) No (02) Yes, sometimes
(01) Yes, most of the time (03) Yes, rarely

Section E – Housing conditions & Residential environment | 0 5 | ID Nº | | | |

E. HOUSING CONDITIONS & RESIDENTIAL ENVIRONMENT

In this section I would like to ask you a few questions about your housing conditions and residential environment at different times in your life. We will use the life grid first to look at the different addresses you lived at, noting the times you moved from one place to another.

Interviewer Reminder: Collect general information using the **life grid**, referring to it later when asking questions in Section E.

- **An address is a place where the participant lived for at least 1 YEAR.**

E1 Up until you were 16 years old (incl.) at how many *different* addresses did you live?
(01) Same place (02) (03) (04) (05) (06) (07) (08) (09 or more).. ☐☐

E2 Between the ages of 17 and 30 (incl.) at how many *different* addresses did you live?
(01) Same place (02) (03) (04) (05) (06) (07) (08) (09 or more)... ☐☐

E3 From the age of 30 (excl.) until today at how many *different* addresses did you live?
(01) Same place (02) (03) (04) (05) (06) (07) (08) (09 or more)... ☐☐
If the respondent is less than 30 years old, mark (88) and GO TO E4

Section E – Housing conditions & Residential environment | 0 5 | ID Nº

CHILDHOOD RESIDENCE

I would like to ask you a few questions about the residence/home in which you lived **for the longest time during your childhood**. By childhood I mean up to age 16 (incl.).

Interviewer Reminder: Identify and confirm longest residence in childhood using the life grid.

E4 You lived at that place...?

From age? **To age?** **i.e. # Years**

For all the following questions, refer to the situation that was present "MOST OF THE TIME" while living in that residence.

E5 What type of setting were you living in at that place?.....
(01) With family (03) Other, specify: _____
(02) Hostel/Orphanage (GO TO E35)
(99) Don't know

E6 Was your home owned or rented?.....
(01) Owned (99) Don't know
(02) Rented (03) Other, specify: _____...

E7 How many people lived in the household?.....
(99) Don't know

Count the number of people at once, for the longest period of time. Include permanent residents including borders, live-in maids, roommates…

E8 How many rooms did your place have?
(99) Don't know

-Include: kitchen, living room, dining room, bedroom, furnished basement
-Do not include: toilet, bathrooms, laundry room, hallway, garage, patio
-If renovated, count # rooms during longest period living there

E9 How many rooms did your household use for sleeping?.....
(99) Don't know

Section E – Housing conditions & Residential environment | 0 5 | ID Nº | | | |

Interviewer Reminder:
- To save time, do not read out all the options for questions E10 to E15.
- Allow the subject to respond and then check the appropriate box.

E10 What was the main material of the floor?.....

(01) Mud/Clay/Earth
(02) Sand
(03) Dung
(04) Raw wood planks
(05) Palm/Bamboo
(06) Brick
(07) Stone
(08) Parquet or polished wood
(09) Vinyl or Asphalt
(10) Ceramic Tiles
(11) Cement
(12) Carpet
(13) Polished stone/Marble/Granite
(14) Other, specify:_____
(99) Don`t know

E11 What was the main material of the roof?.....

(01) No roof
(02) Thatch/Palm leaf/Reed/Grass
(03) Sod/Mud and Grass Mixture
(04) Plastic/Polythene sheeting
(05) Palm/Bamboo
(06) Raw wood planks/Timber
(07) Loosely packed stone
(08) Metal/GI
(09) Wood
(10) Calamine/Cement Fiber
(11) Asbestos Sheets
(12) RCC/RBC/Cement/Concrete
(13) Slate
(14) Other, specify:_____
(99) Don`t know

E12 What was the main material of the exterior walls?.....

(01) No walls
(02) Cane/Palm/Trunks/Bamboo
(03) Mud
(04) Grass/Reeds/Thatch
(05) Bamboo with mud
(06) Stone with mud
(07) Plywood
(08) Cardboard
(09) Unburnt brick
(10) Raw wood/Reused wood
(11) Cement/Concrete
(12) Stone with lime/Cement
(13) Burnt bricks
(14) Cement blocks
(15) Wood planks/Shingles
(16) GI/Metal Asbestos sheets
(17) Other, specify:_____
(99) Don`t know

E13 What type of windows were there?.....

(01) No windows
(02) Windows with glass
(03) Windows with screen
(04) Windows with curtains or shutters
(05) Windows with no glass, screen or cover
(06) Other, specify:_____
(99) Don`t know

Section E – Housing conditions & Residential environment | 0 5 | ID Nº | | | |

Now, I will read a list of facilities you may have had in the place where you lived. We would like to know **which of these facilities were present inside your childhood residence and some details about them.**

E14 What was the main source of <u>drinking</u> water for members of your household? ☐☐

(01) Piped water into dwelling
(02) Piped water to yard/ plot
(03) Piped water (public tap/standpipe)
(04) Tube well or borehole
(05) Dug well (protected)
(06) Dug well (unprotected)
(07) Water from protected spring
(08) Water from unprotected spring
(09) Rainwater
(10) Tanker truck
(11) Cart with small tank
(12) Surface water (river, dam, lake, pond, stream, canal
(13) Bottled water
(99) Don`t know

E15 How many toilet facilities did you have? ..... ☐☐

(99) Don`t know (00) None (GO TO E18)

E16 What kind of toilet facility did members of your household usually use? ..... ☐☐

(01) Flush to piped sewer system
(02) Flush to septic tank
(03) Flush to pit latrine
(04) Flush to somewhere else
(05) Ventilated improved pit/ biogas latrine
(06) Pit latrine with slab
(07) Pit latrine without slab/ open pit
(08) Twin pit/ composting toilet
(09) Dry toilet
(10) Other, specify _____
(99) Don`t know

E17 Did you share this toilet facility with other households?..... ☐☐

(00) No (99) Don't know
(01) Yes

E18 Did your home have electricity?..... ☐☐

(00) No (02) Yes, by a generator/ battery only
(01) Yes, by a central system (99) Don`t know

E19 What type of fuel did your household mainly use for cooking?..... ☐☐

(01) Electricity (GO TO E22) (05) Coal/lignite (09) Agricultural crop waste
(02) LPG/ Natural gas (GO TO E22) (06) Charcoal (10) Dung cakes
(03) Biogas (GO TO E22) (07) Wood (11) Other, specify:_____
(04) Kerosene (GO TO E22) (08) Straw/Shrubs/Grass (99) Don't know

E20 Did the stove have a chimney? ..... ☐☐

(00) No (01) Yes (99) Don't know

E21 Was the stove located in an area with any ventilation/windows?... ..... ☐☐

(00)No (01)Yes (99) Don't know

20

Section E – Housing conditions & Residential environment 0 5 ID Nº

E22 Where was the cooking usually done?.....
(01) Inside the house (02) Separate building (03) Outdoors
(99) Don`t know

E23 Did your home have a separate room which was used as a kitchen?.....
(00) No (01) Yes (99) Don't know

E24 Were you exposed to cigarette smoke in this house?.....
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

I will now read a **list of household goods** you may have had in your childhood residence or not. You may find that some of these appliances were not applicable to the epoch you were a child. Choose the answer that best represents your situation, regardless.

E25 Did your place have a watch or clock?.....
(00) No (01) Yes (99) Don't know

E26 Did your place have a radio or transistor?.....
(00) No (01) Yes (99) Don't know

E27 Did your place have a TV? .....
(00) No (02) Yes, color
(01) Yes, black and white (99) Don't know

E28 Did your place have a refrigerator?.....
(00) No, it had no appliance to cool food (01) Yes
(99) Don't know

Also, I would like to ask you...

E29 Did your household have a bicycle?.....
(00) No (01) Yes (99) Don't know

E30 Did your household have a motorcycle or scooter?.....
(00) No (01) Yes (99) Don't know (GO TO E32)

E31 How many?.....

E32 Did your household have a car?.....
(00) No (01) Yes (99) Don't know (GO TO E34)

E33 How many?.....

Section E – Housing conditions & Residential environment | 0 5 | ID Nº | | | |

E34 Is this childhood residence the same one as the longest residence between ages of 17-30…….. | |

(00) No

(01) Yes, same as the longest residence between ages of 17-30 (Please still fill out the section entitled 'Longest Residence in Early Adult Life')

(02) Yes, the same residence in my whole life (Please still fill out the sections entitled 'Longest Residence in Early Adult Life' and 'Longest Residence in Late Adult Life')

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LONGEST RESIDENCE IN EARLY ADULT LIFE (17-30 yrs)

Now I would like to ask you a few questions about the residence/home in which you lived **for the longest time during your early adult life, that is between the ages of 17 (incl.) and 30 (incl.)**. I will use the same set of question I used in the previous sections.

Interviewer Reminder: Identify / confirm longest residence in early adulthood using life grid.

E35 You lived at that place...?

From age? **To age?** **i.e. # Years**

For all the following questions, refer to the situation that was present "MOST OF THE TIME" while living in that residence.

E36 What type of setting were you living in at that place?.....
(01) With family (02) Other, specify: _____
(99) Don't know

E37 Was your home owned or rented?.....
(01) Owned (99) Don't know
(02) Rented (03) Other, specify: _____...

E38 How many people lived in the household?.....
(99) Don't know

Count the number of people at once, for the longest period of time. Include permanent residents including borders, live-in maids, roommates…

E39 How many rooms did your place have?.....
(99) Don't know

-Include: kitchen, living room, dining room, bedroom, furnished basement
-Do not include: toilet, bathrooms, laundry room, hallway, garage, patio
-If renovated, count # rooms during longest period living there

E40 How many rooms did your household use for sleeping?.....
(99) Don't know

Section E – Housing conditions & Residential environment | 0 5 | ID Nº | | | |

Interviewer Reminder:
- To save time, do not read out all the options for questions E41 to E47.
- Allow the subject to respond and then check the appropriate box.

E41 What was the main material of the floor?.....

(01) Mud/Clay/Earth
(02) Sand
(03) Dung
(04) Raw wood planks
(05) Palm/Bamboo
(06) Brick
(07) Stone
(08) Parquet or polished wood
(09) Vinyl or Asphalt
(10) Ceramic Tiles
(11) Cement
(12) Carpet
(13) Polished stone/Marble/Granite
(14) Other, specify:_____
(99) Don`t know

E42 What was the main material of the roof?.....

(01) No roof
(02) Thatch/Palm leaf/Reed/Grass
(03) Sod/Mud and Grass Mixture
(04) Plastic/Polythene sheeting
(05) Palm/Bamboo
(06) Raw wood planks/Timber
(07) Loosely packed stone
(08) Metal/GI
(09) Wood
(10) Calamine/Cement Fiber
(11) Asbestos Sheets
(12) RCC/RBC/Cement/Concrete
(13) Slate
(14) Other, specify:_____
(99) Don`t know

E43 What was the main material of the exterior walls?.....

(01) No walls
(02) Cane/Palm/Trunks/Bamboo
(03) Mud
(04) Grass/Reeds/Thatch
(05) Bamboo with mud
(06) Stone with mud
(07) Plywood
(08) Cardboard
(09) Unburnt brick
(10) Raw wood/Reused wood
(11) Cement/Concrete
(12) Stone with lime/Cement
(13) Burnt bricks
(14) Cement blocks
(15) Wood planks/Shingles
(16) GI/Metal Asbestos sheets
(17) Other, specify:_____
(99) Don`t know

E44 What type of windows were there?.....

(01) No windows
(02) Windows with glass
(03) Windows with screen
(04) Windows with curtains or shutters
(05) Windows with no glass, screen or cover
(06) Other, specify:_____
(99) Don`t know

Section E – Housing conditions & Residential environment | 0 5 | ID Nº

Now, I will read a list of facilities you may have had in the place where you lived. We would like to know **which of these facilities were present inside your early adulthood (17-30 yrs) residence and some details about them.**

E45 What was the main source of <u>drinking</u> water for members of your household?
(01) Piped water into dwelling
(02) Piped water to yard/ plot
(03) Piped water (public tap/standpipe)
(04) Tube well or borehole
(05) Dug well (protected)
(06) Dug well (unprotected)
(07) Water from protected spring
(08) Water from unprotected spring
(09) Rainwater
(10) Tanker truck
(11) Cart with small tank
(12) Surface water (river, dam, lake, pond, stream, canal
(13) Bottled water
(99) Don`t know

E46 How many toilet facilities did you have? .....
(99) Don`t know (00) None (GO TO E49)

E47 What kind of toilet facility did members of your household usually use? .....
(01) Flush to piped sewer system
(02) Flush to septic tank
(03) Flush to pit latrine
(04) Flush to somewhere else
(05) Ventilated improved pit/ biogas latrine
(06) Pit latrine with slab
(07) Pit latrine without slab/ open pit
(08) Twin pit/ composting toilet
(09) Dry toilet
(10) No facilities
(11) Other, specify _____
(99) Don`t know

E48 Did you share this toilet facility with other households?.....
(01) No (99) Don't know
(01) Yes

E49 Did your home have electricity?.....
(00) No (02) Yes, by a generator/ battery only
(01) Yes, by a central system (99) Don`t know

E50 What type of fuel did your household <u>mainly</u> use for cooking?.....
(01) Electricity (GO TO E53)
(02) LPG/ Natural gas (GO TO E53)
(03) Biogas (GO TO E53)
(04) Kerosene (GO TO E53)
(05) Coal/lignite
(06) Charcoal
(07) Wood
(08) Straw/Shrubs/Grass
(09) Agricultural crop waste
(10) Dung cakes
(11) Other, specify:_____
(99) Don't know

E51 Did the stove have a chimney? .....
(00) No (01) Yes (99) Don't know

E52 Was the stove located in an area with any ventilation/windows?... .....
(00)No (01)Yes (99) Don't know

E53 Where was the cooking usually done?.....
(01) Inside the house (02) Separate building (03) Outdoors
(99) Don`t know

Section E – Housing conditions & Residential environment | 0 5 | ID Nº

E54 Did your home have a separate room which was used as a kitchen?.....
(00) No (01) Yes (99) Don't know

E55 Were you exposed to cigarette smoke in this house?.....
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

I will now read a **list of household goods** you may have had in your early adulthood (17-30 yrs) residence or not. You may find that some of these appliances were not applicable to the epoch you were a child. Choose the answer that best represents your situation, regardless.

E56 Did your place have a watch or clock?.....
(00) No (01) Yes (99) Don't know

E57 Did your place have a radio or transistor?.....
(00) No (01) Yes (99) Don't know

E58 Did your place have a TV? .....
(00) No (02) Yes, color
(01) Yes, black and white (99) Don't know

E59 Did your place have a refrigerator?.....
(00) No, it had no appliance to cool food (02) Yes
(01) No, it had an ice box (99) Don't know

Also, I would like to ask you...

E60 Did your household have a bicycle?.....
(00) No (01) Yes (99) Don't know

E61 Did your household have a motorcycle or scooter?.....
(00) No (01) Yes (99) Don't know (GO TO E62)

E62 How many?.....

E63 Did your household have a car?.....
(00) No (01) Yes (99) Don't know (GO TO E64)

E64 How many?.....

Section E – Housing conditions & Residential environment | 0 5 | ID Nº

LONGEST RESIDENCE IN LATER ADULTHOOD (30 yrs+)

Now lets talk about your **longest residence in later adulthood**, that is after age 30 (excl.).

Interviewer Reminder: Identify / confirm longest residence in later adulthood using life grid.

E65 Is this residence the same one as the residence you lived in for the longest time between the ages of 17 and 30 or your childhood residence?.....

(00) No (01) Yes, same as longest residence between ages of 17-30 (Please still fill out the section entitled 'Longest Residence in Late Adult Life')
(02) Yes, same as childhood residence 30 (Please still fill out the section entitled 'Longest Residence in Late Adult Life')
(88) None of the above : ex: Subject is less than 30 yrs old (GO TO SECTION F)

E66 You lived at that place...?

From age? **To age?** **i.e. # Years**

For all the following questions, refer to the situation that was present "MOST OF THE TIME" while living in that residence.

E67 What type of setting were you living in at that place?.....
(01) With family (02) Other, specify: _____
(99) Don't know

E68 Was your home owned or rented?.....
(01) Owned (99) Don't know
(02) Rented (03) Other, specify: _____... _____

E69 How many people lived in the household? (At once, for the longest period of time)…
(Include borders, live-in maids, roommates...) (99) Don't know

Count the number of people at once, for the longest period of time. Include permanent residents including borders, live-in maids, roommates…

E70 How many rooms did your place have? (If renovated, count # rooms during longest period living there)……
(99) Don't know

-Include: kitchen, living room, dining room, bedroom, furnished basement
-Do not include: toilet, bathrooms, laundry room, hallway, garage, patio
-If renovated, count # rooms during longest period living there

E71 How many rooms did your household use for sleeping?.....
(99) Don't know

Section E – Housing conditions & Residential environment | 0 5 | ID Nº | | | |

Interviewer Reminder:
- To save time, do not read out all the options for questions E72 to E78.
- Allow the subject to respond and then check the appropriate box.

E72 What was the main material of the floor?.....

(01) Mud/Clay/Earth
(02) Sand
(03) Dung
(04) Raw wood planks
(05) Palm/Bamboo
(06) Brick
(07) Stone
(08) Parquet or polished wood
(09) Vinyl or Asphalt
(10) Ceramic Tiles
(11) Cement
(12) Carpet
(13) Polished stone/Marble/Granite
(14) Other, specify:_____
(99) Don`t know

E73 What was the main material of the roof?.....

(01) No roof
(02) Thatch/Palm leaf/Reed/Grass
(03) Sod/Mud and Grass Mixture
(04) Plastic/Polythene sheeting
(05) Palm/Bamboo
(06) Raw wood planks/Timber
(07) Loosely packed stone
(08) Metal/GI
(09) Wood
(10) Calamine/Cement Fiber
(11) Asbestos Sheets
(12) RCC/RBC/Cement/Concrete
(13) Slate
(14) Other, specify:_____
(99) Don`t know

E74 What was the main material of the exterior walls?.....

(01) No walls
(02) Cane/Palm/Trunks/Bamboo
(03) Mud
(04) Grass/Reeds/Thatch
(05) Bamboo with mud
(06) Stone with mud
(07) Plywood
(08) Cardboard
(09) Unburnt brick
(10) Raw wood/Reused wood
(11) Cement/Concrete
(12) Stone with lime/Cement
(13) Burnt bricks
(14) Cement blocks
(15) Wood planks/Shingles
(16) GI/Metal Asbestos sheets
(17) Other, specify:_____
(99) Don`t know

E75 What type of windows were there?.....

(01) No windows
(02) Windows with glass
(03) Windows with screen
(04) Windows with curtains or shutters
(05) Windows with no glass, screen or cover
(06) Other, specify:_____
(99) Don`t know

Section E – Housing conditions & Residential environment | 0 5 | ID Nº

Now, I will read a list of facilities you may have had in the place where you lived. We would like to know **which of these facilities were present inside your late adulthood (30+ yrs) residence and some details about them.**

E76 What was the main source of <u>drinking</u> water for members of your household?
(01) Piped water into dwelling
(02) Piped water to yard/ plot
(03) Piped water (public tap/standpipe)
(04) Tube well or borehole
(05) Dug well (protected)
(06) Dug well (unprotected)
(07) Water from protected spring
(08) Water from unprotected spring
(09) Rainwater
(10) Tanker truck
(11) Cart with small tank
(12) Surface water (river, dam, lake, pond, stream, canal
(13) Bottled water
(99) Don`t know

E77 How many toilet facilities did you have? .....
(99) Don`t know (00) None (GO TO E80)

E78 What kind of toilet facility did members of your household usually use? .....
(01) Flush to piped sewer system
(02) Flush to septic tank
(03) Flush to pit latrine
(04) Flush to somewhere else
(05) Ventilated improved pit/ biogas latrine
(06) Pit latrine with slab
(07) Pit latrine without slab/ open pit
(08) Twin pit/ composting toilet
(09) Dry toilet
(10) No facilities
(11) Other, specify _____
(99) Don`t know

E79 Did you share this toilet facility with other households?.....
(00) No (99) Don't know
(01) Yes

E80 Did your home have electricity?.....
(00) No (02) Yes, by a generator/ battery only
(01) Yes, by a central system (99) Don`t know

E81 What type of fuel did your household mainly use for cooking?.....
(01) Electricity (GO TO E84) (05) Coal/lignite (09) Agricultural crop waste
(02) LPG/ Natural gas (GO TO E84) (06) Charcoal (10) Dung cakes
(03) Biogas (GO TO E84) (07) Wood (11) Other, specify:_____
(04) Kerosene (GO TO E84) (08) Straw/Shrubs/Grass (99) Don't know

E82 Did the stove have a chimney? .....
(00) No (01) Yes (99) Don't know

E83 Was the stove located in an area with any ventilation/windows?... .....
(00)No (01)Yes (99) Don't know

Section E – Housing conditions & Residential environment | 0 5 | ID Nº

E84 Did your home have a separate room which was used as a kitchen?.....
(00) No (01) Yes (99) Don't know

E85 Were you exposed to cigarette smoke in this house?.....
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

I will now read a **list of household goods** you may have had in your late adulthood (30+ yrs) residence or not. You may find that some of these appliances were not applicable to the epoch you were a child. Choose the answer that best represents your situation, regardless.

E86 Did your place have a watch or clock?.....
(00) No (01) Yes (99) Don't know

E87 Did your place have a radio or transistor?.....
(00) No (01) Yes (99) Don't know

E88 Did your place have a TV? .....
(00) No (02) Yes, color
(01) Yes, black and white (99) Don't know

E89 Did your place have a telephone?.....
(00) No (01) Yes (99) Don't know

E90 Did your place have a refrigerator?.....
(00) No, it had no appliance to cool food (02) Yes
(01) No, it had an ice box (99) Don't know

Also, I would like to ask you...

E91 Did your household have a bicycle?.....
(00) No (01) Yes (99) Don't know

E92 Did your household have a motorcycle or scooter?.....
(00) No (01) Yes (99) Don't know (GO TO E94)

E93 How many?.....

E94 Did your household have a car?.....
(00) No (01) Yes (99) Don't know (GO TO SECTION F)

E95 How many?.....

Section F – Smoking and Chewing habits | 0 5 Country | ID N°

F. SMOKING AND CHEWING HABITS

Now I would like to ask you some questions about your smoking and/or chewing habits.

F1 Have you ever smoked in your life? (or chewed, any product, any amount)……..
(00) Never (GO TO F6) (01) Yes (I still do) (02) Yes, but only in the past

Think of the periods in your life during which you smoked cigarettes, cigars, pipe, chewed tobacco products and/or took drugs, the amount you smoked/chewed/took and other details about the products. Please try to summarise the most important changes in the amount and type of product.

Interviewer Reminder: Use **life grid** if necessary to help answer Q F2 to F8.
- Avoid overlapping years for the same product, type of cigarette or amount smoked, i.e. record 30-40, 41-45 rather than 30-40, 40-45.
- Only note changes occurring for **one year or more**.
- Exclude quitting during pregnancy(ies) if for less than one year.

F2 Do/did you smoke cigarettes?.....
(00) No (GO TO F3) (01) Yes (02) Yes, only in the past

From age	To age (A)	Type (B)	Brand	Consumption (how many)	Per (C)

To Age (A)	Type (B)	Per (C)
If still smoking, write age at time of interview	(01) Filter (02) Non-filter (03) Hand rolled	(01) Day (02) Week (03) Month

Section F – Smoking and Chewing habits | 0 5 Country | ID N°

F3 Do/did you smoke bidis?.....
(00) No (GO TO F8) (01) Yes (02) Yes, only in the past

From age	To age (A)	Consumption (how many)	Per (C)

To Age (A)	Per (C)
If still using, write age at time of interview	(01) Day (02) Week (03) Month

F4 Do/did you smoke or inhale drugs (marijuana, grass, dope, joints...) at least once a week for at least 6 months in your lifetime?.....
(00) No (GO TO F6) (01) Yes (02) Yes, only in the past

From age	To age (A)	Type (B)	Unit	Consumption (how many)	Per (C)

To Age (A)	Type (B)	Unit (C)	Per (C)
If still smoking, write age at time of interview If less than one year, write same age From and To	(01) Marijuana (02) Grass (03) Crack (04) Hashish	(01) Grams (02) Joints	(01) Day (02) Week (03) Month

Section F – Smoking and Chewing habits

0	5				
Country		ID N°			

F5 Do/did you <u>use any other drugs</u> (cocaine, heroin, lsd...) at least once a week for at least 6 months in your lifetime?..... ☐☐

(00) No (GO TO Section G) (01) Yes (02) Yes, only in the past

From age	To age (A)	Type (B)	Unit	Consumption (how many)	Per (C)
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐☐	☐☐	☐☐

To Age (A)	Type (B)	Unit (C)	Per (C)
If still using, write age at time of interview If less than one year, write same age From and To	(01) Cocaine (02) Acid / LSD (03) Heroin (04) Opium (05) Brown sugar powder (06) Churut (07) Ghutka	(01) Grams (02)Joints (03)Injections (04) Pills	(01) Day (02) Week (03) Month

Section F – Smoking and Chewing habits

0	5			
Country		ID N°		

F6 Do/did you use chewing tobacco, betel quid (nut), areca nut and/or pan masaala? ☐☐

(00) No (GO TO SECTION G) (01) Yes (02) Yes, only in the past

From age	To age (A)	Type (B)	Duration	Consumption (how many)	Per (C)
☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐
☐☐	☐☐	☐☐	☐	☐☐	☐☐

Interviewer Reminder: Betel Quid = areca nut + betel leaf + slaked lime

To Age (A)	**Type (B)**	**Per (C)**
If still smoking, write age at time of interview	(01) Tobacco (02) Betel quid (nut) with tobacco (03) Betel quid (nut) without tobacco (04) Areca nut with tobacco (05) Areca nut without tobacco (06) Pan masalla (07) Betel leaf (08) Other, specify_____	(01) Day (02) Week (03) Month y

F7 What is the reason that you began chewing tobacco, betel quid (nut), areca nut and/or pan masaala?..... ☐☐

(01) Toothaches (02) Enjoyment

(03) Mouth freshener (88) Not applicable

Section G – Drinking habits | 0 5 Country | ID N°

G. DRINKING HABITS

Now I would like to ask you some questions about your drinking habits.

G1 Did/do you drink alcoholic beverages <u>at least once a month</u>?.....

(00) No (GO TO SECTION H) (01) Yes, I do (02) Yes, only in the past

We can use the grid to help us describe the periods in your life during which you consumed alcoholic beverages. Please try to summarise the most important changes in your life regarding the amount and type of beverage.

Interviewer Reminder: Use **life grid** if necessary to help answer Q G3.

- Avoid overlapping years for the same beverage i.e. record 30-40, 41-45 rather that 30-40, 40-45. Ask about each beverage separately.
- Note only changes occurring for **<u>one year or more</u>.**
- Exclude quitting during pregnancy(ies) if for less than one year.

G2 When do/did you usually drink alcoholic beverages?.....

(01) With meals (03) Both

(02) Between meals (04) Only at social events

G3 Beverage (A)	If (A) = (05), Then specify other beverage	From age	To age	Unit (B)	Consumption (how many)	Per (C)

Beverage (A)
(01) Toddy
(02) Wine
(03) Beer
(04) Hard liquor (>35) (arak, whisky, cognac, vodka, brandy, grappa, marc, gin, rum)
(05) Other (specify): _____

Unit (B)
(01) Small glass (50ml) (1-2oz)
(02) Medium glass (100ml) (2-3oz)
(03) Big glass (250ml) (7oz) (1/2 pint)
(04) ½ small bottle (330ml) (1beer)
(05) Bottle (700-750 ml) (21oz)

Per (C)
(01) Day
(02) Week
(03) Month

35

Section H – Dietary habits | 0 5 Country | ID N°

H. DIETARY HABITS

Now, I have some questions about your dietary habits during your childhood (up to 16 years old).

H1 How many large meals did you normally eat per day in your childhood (up to 16 years old)?

(01) 1 (03) 3
(02) 2 (04) 4 or more (99) I don't know

H2 During your childhood (up to 16 years old), how often did you eat the following foods?

		Never	Occasionally	Weekly	Daily
H2a	**Bananas**				
H2b	**Citrus fruits** (e.g., oranges, grapefruits)				
H2c	**Apples/ Pears**				
H2d	**Other fruits** (e.g., mango, jackfruit, papaya, pineapple)				
H2e	**Raw vegetables**				
H2f	**Cooked vegetables** (e.g., in a curry)				
H2g	**Sweet potato**				
H2h	**Tapioca**				
H2i	**Red meat** (e.g., beef, mutton)				
H2j	**White meat** (e.g., chicken, turkey)				
H2k	**Fish**				
H2l	**Dairy products** (e.g., milk, yogurt, curd, cheese)				
H2m	**Nuts** (e.g., cashews)				
H2n	**Dals**				
H2o	**Rice**				
H2p	**Appam**				
H2q	**Flat breads** (e.g., chapati , porotta)				
H2r	**Dosa & Idly**				
H2s	**Gruel & cereal**				
H2t	**Palm products** (e.g. palm rice)				
H2u	**Fried foods** (e.g., chips, fried fish, fried chicken)				
H2v	**Desserts** (e.g., chocolate)				
H2w	**Sugary drinks** (e.g. soda, juice)				

Section H – Dietary habits | 0 5 Country | ID N°

As your dietary habits may have recently changed somewhat according to your health status, **please tell me about your usual habits approximately 2 years prior to your diagnosis of the disease / being seen at this clinic**.

H3 How many large meals did you normally eat per day in your adult life?

(01) 1 (03) 3
(02) 2 (04) 4 or more (99) I don't know

H4 During your adulthood (approx. 2 years prior to your diagnosis), please tell me how often you ate the following foods per week.

		Never	<Once per week	# times per week
H4a	**Bananas**			
H4b	**Citrus fruit** (e.g., oranges, lemons, grapefruit)			
H4c	**Apples/pears**			
H4d	**Other fruits** (e.g., mango, jackfruit, papaya, pineapple)			
For the following vegetables, please specify the amount eaten raw and/or cooked				
H4e	**Cruciferous vegetables** (e.g., cabbage, cauliflower)			
H4f	**Yellow-orange vegetables** (e.g., tomatoes, carrots, pumpkin)			
H4g	**Spinach**			
H4h	**Other vegetables** (e.g., cucumber, onions)			
H4i	**Sweet potato**			
H4j	**Tapioca**			
H4k	**Red meat** (e.g., beef, mutton)			
H4l	**White meat** (e.g., chicken, turkey)			
H4m	**Fish**			
H4n	**Milk**			
H4o	**Other Dairy products** (e.g., yogurt, curd, cheese)			
H4p	**Nuts** (e.g., cashews)			
H4q	**Dals**			
H4r	**Rice**			
H4s	**Appam**			
H4t	**Flat breads** (e.g., chapati , porotta)			
H4u	**Dosa & Idly**			
H4v	**Gruel & Cereal**			
H4w	**Palm products** (e.g., palm rice)			
H4x	**Fried foods** (e.g., banana chips, chips, fried fish, fried chicken)			
H4y	**Desserts** (e.g., chocolate)			
H4z	**Sugary drinks** (e.g. soda, juice)			

Section H – Dietary habits | 0 5 Country | ID N°

Please answer the following questions based on your usual habits approximately 2 years prior to your diagnosis of the disease / being seen at this clinic.

H5 Did you eat foods which are?

(01) Not spicy at all
(02) A little spicy
(03) Moderately spicy
(04) Very spicy
(99) I don't know

H6 Did you eat foods which have ?

(01) No chile
(02) A little chile
(03) Moderate amount of chile
(04) A lot of chile
(99) I don't know

H7 Please tell me how often did you eat the following spices?

		Never	<once per week	# per week
H7a	**Chile**			
H7b	**Red chile**			
H7c	**Coriander**			
H7d	**Garam Masala**			
H7e	**Pepper**			
H7f	**Turmeric**			
H7g	**Ginger**			

H8 Did you reuse your oil?.....
(00) No (01) Yes

H9 If yes, how many times?.....
(00) Once (01) Twice (03) More than 2 times

H10 How many cups of coffee did you drink per day?.....
(00) I didn't drink coffee (98) Less than one a day

H11 How many cups of tea did you drink per day?.....
(00) I didn't drink tea (98) Less than one a day

H12 How did you usually drink your tea/coffee?.....
(00) I didn't drink tea/coffee (01) Hot (02) Warm (03) Cold

Section H – Dietary habits | 0 5 Country | ID N°

BODY IMAGE

CHILDHOOD

Think about your appearance when you were a CHILD (5-6 years old, when you had just started school) and compare it to other children your age.

APPEARANCE:

H13 When you were a child (5-6 years old); were you?.....
(01) much slimmer than other children your age
(02) slimmer
(03) similar
(04) heavier
(05) much heavier than other children your age
(99) I don't know

HEIGHT

H14 When you were a child (5-6 years old); were you?.....
(01) much shorter than other children your age
(02) shorter
(03) similar
(04) taller
(05) much taller than other children your age
(99) I don't know

H15 Which of the following silhouettes (1 to 9) resembles your appearance when you were 5-6 years of age?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

ADOLESCENCE

Think about your appearance when you were an ADOLESCENT (12-15 years old) and compare it to other adolescents your age.

APPEARANCE:

H16 When you were an adolescent (12-15 years old); were you?.....
(01) much slimmer than other adolescents your age
(02) slimmer
(03) similar
(04) heavier
(05) much heavier than other adolescents your age
(99) I don't know

Section H – Dietary habits | 0 5 Country | ID N°

HEIGHT

H17 When you were an adolescent (12-15 years old); were you?.....
(01) much shorter than other adolescents your age
(02) shorter
(03) similar
(04) taller
(05) much taller than other adolescents your age
(99) I don't know

H18 Which of the following silhouettes (1 to 9) resembles your appearance when you were 12-15 years of age?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

EARLY ADULTHOOD

Think about your appearance when you were an EARLY ADULT (17-30 years old).

H19 Which of the following silhouettes (1 to 9) resembles your appearance when you were 17-30 years of age?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

LATE ADULTHOOD

Think about your appearance when you were an LATER ADULT (30+ years old).

H20 Which of the following silhouettes (1 to 9) resembles your appearance when you were 30+ years of age?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

2 YEARS AGO

Think about your appearance 2 YEARS AGO.

H21 Which of the following silhouettes (1 to 9) resembles your appearance 2 years ago?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

PRESENT

Think about your appearance PRESENTLY.

H22 Which of the following silhouettes (1 to 9) resembles your appearance presently?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

Section H – Dietary habits | 0 5 Country | ID N°

INTERVIEWER REMINDER: Weight measurement
Weigh the participant using the HeNCe Life study scale provided. Measurement should be done in **kgs**, but if it is done in **lbs**, convert the measurement to **kgs** as specified below.

H23 Weight measurement?
(_____ lbs) ÷ 2.2042 = _____**kgs**

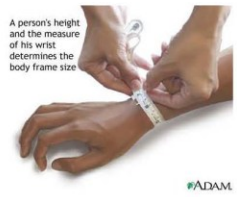
INTERVIEWER REMINDER: Height measurement
Measure the participant using the measuring tape provided in the HeNCe Life study package. The participant must be positioned with their
-feet together and flat on the ground
-heels touching the wall
-legs straight
-buttocks against the wall
-arms loosely at their side
-ensure that their feet and heels do not raise up off the ground
Measurement should be done in **cms**, but if it is done in **inches**, convert the measurement to **cms** as specified below. You may find it easier to ask someone to help you take the measurement.

H24 Height measurement? .....
(___feet ___ inches) = _____inches x 2.54 = _____**cm**

INTERVIEWER REMINDER: Finger measurements
Please ask the participant to lay their **right hand** on the table palm-up, with the fingers fully extended. Measure the lengths of both the index finger (2nd finger) and the ring finger (4th finger). ***Note: the thumb is considered the 1st finger.*** The measurement should be taken from the tip of the finger to the lowest (most proximal) crease using the ruler provided in the HeNCe Life package. The index finger usually has only one proximal crease, whereas the ring finger sometimes has two.

H25 Finger measurements (right hand)? .....
Index (2^{nd} finger):_____ cm (1 decimal)
Ring finger (4^{th} finger): _____ cm (1 decimal)

H26 Wrist measurement? .....
Around the small of the right wrist:_____ inches (1 decimal)



Section H – Dietary habits | 0 5 Country | ID N°

H27 What sized body frame does the subject have?

Please refer to the Interviewer's Guide for coding

(01) small body frame
(02) medium body frame
(03) large body frame
(04) man under 165 cm height

H28 When you're AT WORK (include work as a housewife), which of the following best describes your level of activity?

(01) Very active (e.g., farmer, labourer, athlete)
(02) Moderately active
(03) Sedentary (e.g., desk job)
(04) I don't work
(99) I don't know

H29 When you're AT HOME, which of the following best describes your level of activity?

(01) Very active
(02) Moderately active
(03) Sedentary
(99) I don't know

H30 DURING LEISURE TIME, which of the following best describes your level of activity?

(01) Very active
(02) Moderately active
(03) Sedentary
(99) I don't know

Section I – Oral health | 0 5 Country | ID Nº

I. ORAL HEALTH

I am going to ask you some questions about your oral health **before your diagnosis / being seen at this clinic** and at different time in your lifetime.

I1 Did you wear complete dentures? .....
(00) No (GO TO I4) (02) Yes, top only
(01) Yes, bottom only (GO TO I3) (03) Yes, top AND bottom

I2 At what age did you start wearing complete top dentures? (Years).....

I3 At what age did you start wearing complete bottom dentures? (Years).....
Code (888) if QI1 = (02)

I4 Did you wear partial dentures?.....
(00) No (02) Yes, bottom only
(01) Yes, top only (03) Yes , top AND bottom

I5 How often did you clean your teeth?.....
(00) Never (03) Every other day
(01) Less than once a week (04) Once a day
(02) 1-2 time a week (05) Twice or more a day

I6 Did you use toothpicks / sticks?.....
(00) No (02) Yes, once a week
(01) Yes, daily (03) Rarely

I7 Did you use any kind of substance to clean your teeth?.....
(00) No (02) Charcoal
(01) Toothpaste (03) Other (specify)_____.....

I8 Did your gums bleed when you cleaned your teeth?.....
(00) No (01) Sometimes (02) Always or almost always

Now, let's look at your oral health habits and oral health at different periods of your life.

I9 In the <u>last 20 years</u>, how often did you see a dentist?.....
(00) Never (03) Every 2 –5 years
(01) Every 6 months (04) Once every 5 years
(02) Every year (05) Only when I had pain

I10 Have you ever had an ulcer or a cut in your cheek because of a tooth or dentures?
(00) No (01) Yes

Section J – Family history of cancer | 0 5 Country | ID N°

J. FAMILY HISTORY OF CANCER

Interviewer Reminder:
- Family includes these **biological** relatives: father, mother, brother, sister, son, daughter, aunt, uncle, grand-mother, grand-father.
- Input one person per line in chart below.

J1 Has any member of your biological family ever had cancer? .....
(00) No (GO TO SECTION K) (01) Yes (99) Don't know

J2 Relationship (A)	Status (B)	Current/Last Age (C)	Type of cancer	Age at Diagnosis (D)

Relationship (A)	Status (B)	Current / Last Age (C)	Age at diagnosis (D)
(01) Mother (02) Father (03) Sister (04) Brother (05) Daughter (06) Son (07) Grand-mother (08) Grand-father (09) Aunt/uncle	(00) Deceased (01) Alive	(999) Don't know If alive, give present age If deceased, give age at death	(999) Don't know

Section K – Family environment | 0 5 Country | ID N°

K. FAMILY ENVIRONMENT IN CHILDHOOD

I would like to ask you a few questions about your parents (mother and father), or the women or men who cared for you **during your childhood, that is from your birth until you were 16 years (incl.)**. If you were cared for by only one person, please respond only to the questions related to that person. We may refer to the life grid to help us out at times.

This first set of questions is related to their level of education and their occupation.

K1 At your birth, how old was your father?..... ☐☐
(99) Don't know

K2 How many years of education did your father/the man who cared for you most of your childhood have?..... ☐☐
(99) Don't know

K3 What was his longest occupation during your childhood?(LC)..... ☐☐☐
Describe: _____
(999) Don't know

K4 At your birth, how old was your mother?..... ☐☐
(99) Don't know

K5 How many years of education did your mother/the woman who cared for you most of the time during your childhood have?..... ☐☐
(99) Don't know

K6 What was her longest occupation during your childhood? (LC)..... ☐☐☐
Describe: _____
(999) Don't know

Interviewer Reminder: Confirm occupation codes in K3 and K6 with list of codes.

Now I have a few questions on family environment during your childhood.

K7 In total, how many brothers and sisters do you have? (natural only)..... ☐☐

K8 What was your birth order in your family?..... ☐☐
(00) Only child (02) Second child (04) Fourth child or more
(01) First child (03) Third child

K9 Did your family have continuous financial difficulties during your childhood? ☐☐
(00) No (01) Yes (99) Don't know

Section K – Family environment | 0 5 Country | ID N°

K10 Did your parents argue or fight during your childhood?.....
(00) Never (02) Often
(01) Sometimes (99) Don't know

K11 How often did your father use to drink alcohol during your childhood?.....
(00) Never (02) Once a week / weekends (04) Everyday
(01) Occasionally (03) 3-4 times a week (99) Don't know

K12 How often did your mother use to drink alcohol during your childhood?.....
(00) Never (02) Once a week / weekends (04) Everyday
(01) Occasionally (03) 3-4 times a week (99) Don't know

K13 Did your father smoke? (any product).....
(00) No (01) Yes (99) Don't know

K14 Did your mother smoke? (any product) .....
(00) No (01) Yes (99) Don't know

K15 Did your father chew tobacco, betel quid (nut), areca nut, pan masaala or betel leaf?.....
(00) No (01) Yes (99) Don't know

K16 Did your mother chew tobacco, betel quid (nut), areca nut, pan masaala or betel leaf?.....
(00) No (01) Yes (99) Don't know

K17 Were your parents divorced?.....
(00) No (01) Yes (99) Don't know

Now I would like to ask you a few questions about your mother / father figure during your childhood.

K18 Who was the woman who cared for you most of your life during your childhood?.
(00) None (GO TO K25) (03) Adoptive mother
(01) Mother (04) Grand-mother
(02) Step mother (05) Other, specify_____.....

Section K – Family environment | 0 5 Country | ID N°

Here are some questions about how you remember your **MOTHER** (or the woman who cared for you) during the years you were growing up, that is, until you were age 16 – incl. (Use Answer Sheet)

(01) A great deal (02) Quite a lot (03) Little (04) Not at all

K19 How much did she understand your problems and worries?.....

K20 How much could you confide in her about things that were bothering you?....

K21 How much love and affection did she give you?.....

K22 How much time and attention did she give you when you needed it?.....

K23 How strict was she with the rules for you?.....

K24 How harsh was she when she punished you?.....

K25 How much did she expect you to do your best in everything you did?.....

Now I would like to ask you how you remember your **FATHER** (or the man who cared for you) during the years you were growing up that is, until you were 16 years old. (Use Answer Sheet)

K26 Who was the man who cared for you most of your life during your childhood?.....

(00) None (GO TO K33) (03) Adoptive father
(01) Father (04) Grand-father
(02) Step father (05) Other, specify: _____.....

(01) A great deal (02) Quite a lot (03) Little (04) Not at all

K27 How much did he understand your problems and worries?.....

K28 How much could you confide in him about things that were bothering you?...

K29 How much love and affection did he give you?.....

K30 How much time and attention did he give you when you needed it?.....

K31 How strict was he with the rules for you?.....

K32 How harsh was he when he punished you?.....

K33 How much did he expect you to do your best in everything you did?.....

Section K – Family environment | 0 5 Country | ID N°

K34 Can you remember any life event(s) in your childhood that have either positively or negatively impacted upon you?.....
(00) No (GO TO SECTION L) (01) Yes

K35 Can you tell me what? (Describe)**(LC)**.....
1 _____
2 _____
3 _____
4 _____
5 _____

K36 Could you please tell me how much impact this (se) event (s) had on your life?
(Use Answer Sheet).....

-4 -3 -2 -1 0 1 2 3 4
Very negative no impact Very positive

Event 1 ……..score: _____……..
Event 2 ……..score: _____……..
Event 3 ……..score: _____……..
Event 4 ……..score: _____……..
Event 5 ……..score: _____……..

Section K – Family environment | 0 5 Country | ID N°

K37 For each of the following diseases, please tell me if you ever had it and, if so, how often?

Presence (A)	Frequency (B)
(00) No	(01) Once
(01) Yes	(02) Sometimes
(99) Don't know	(03) Often

	Presence (A)	Frequency (B)
Measles		
Mumps		
Chicken pox		
Whooping cough		
Infectious hepatitis		
Jaundice		
Tuberculosis		
Asthma attack		
Disease of the ear(s)		
Disease of the nose		
Disease of the throat		
Depression treated with medication		
Repeated or prolonged infections (>6 weeks)		
Diabetes		

Specify other diseases: (ex. Diabetes, thyroid disease, chronic heartburn, bulimia):

_____ _____

K38 What type of medicine do you use for management of common diseases?

(00) None
(01) Allopathy
(05) Homeopathy
(03) Ayurvedic
(04) Other, specify: _____.....

Section L – Marriage, intimacy and life as a couple | 0 5 Country | ID N°

L. MARRIAGE, INTIMACY & LIFE AS A COUPLE

Now, I would like to ask you some questions about marriage and living as a couple.

L1 What is your marital status?.....

(01) Single (GO TO L8)
(02) Living with a husband/wife (married)
(03) Married, gauna not performed
(04) Married to more than one wife
(05) Living with partner common-law
(06) Widowed
(07) Divorced
(08) Separated
(09) Deserted

INTERVIEWER REMINDER: Use **life grid** if necessary to help answer Q L2 to L26.

L2 How many times have you been married or lived in common law?.....

(01) Once (Fill in first column only) (02) More than once

At the time you FIRST/LAST got married or FIRST/LAST lived in common law...

	FIRST	LAST
L3 How old were you?.....		
L4 How many years did your partner go to school for? (until today)		
L5 What was your partner's longest occupation? (until today) **(LC)**		

FIRST: _____

LAST: _____

L6 How did the relationship end?.....		

(00) Still ongoing! (GO TO L8) (02) Separation
(01) Divorce (03) Partner deceased

L7 How old were you when the relationship ended?.....

L8 In your whole life, how many (biological) children have you had?.....

(00) None (GO TO L13) *(Do NOT include miscarriage or stillborn)*

L9 With how many <u>different</u> partners?.....

(00) All with the same one

L10 Do you have any sons or daughters that you have fathered/mothered that are now living with you?.....

(00) No (01) Yes

L11 How old is your oldest child?.....

(99) Don`t know

Section L – Marriage, intimacy and life as a couple | 0 5 Country | ID N°

L12 How old is your youngest child?.....
(99) Don't know

I will ask you some questions regarding your sexuality. The reason I am asking these questions is because medical science has found some links between viruses that are sexually transmitted and some types of cancers. You have no obligation to answer these questions if you do not feel comfortable doing so.

L13 Have you ever had sexual intercourse?.....
(00) No (GO TO L14) (01) Yes
(99) Prefer not to say / Don't know

L14 How old were you when you had sexual intercourse for the first time?
(99) Prefer not to say / Don't know

Answer's options L15 and L16		
(00) None	(03) 06-10	(06) 51-100
(01) One	(04) 11-20	(07) More than 100
(02) 2-5	(05) 21-50	(99) Prefer not to say / Don't know

L15 How many sexual partners have you had in total in your life? (regular and casual)...
Up to 16 yrs old .....
Between 17-30 yrs old .....
After 30 yrs old .....

L16 How many of these people did you pay in exchange for sex?
Up to 16 yrs old .....
Between 17-30 yrs old .....
More than 30 yrs old .....

L17 Have you ever had oral sex? (your mouth and a woman/man genitals).....
(00) No (GO TO (GO TO L17) (99) Prefer not to say / Don't know (GO TO L17)
(01) Yes

L18 How old were you when you had oral sex for the first time?.....
(99) Prefer not to say / Don't know

Answer's options Q16	
(00) Occasionally	(02) Most of the time
(01) Frequently	(99) Prefer not to say / Don't know

L19 How often? .....
Up to 16 yrs old .....
Between 17-30 yrs old .....
After 30 years old .....

Section L – Marriage, intimacy and life as a couple | 0 5 Country | ID N°

L20 Have you ever had non-consenting sex?.....
(00) No (GO TO (GO TO L19) (99) Prefer not to say / Don't know (GO TO L19)
(01) Yes

L21 How old were you or from what age to what age? *(mark same age if one episode or if during less than one year)* (99) Prefer not to say / Don't know

From age?	**To age?**	**i.e. # Years**

L22 Have you ever had skin warts?.....
(00) No (GO TO (GO TO L22) (99) Prefer not to say / Don't know (GO TO L22)
(01) Yes

L23 If yes, where? (01) Yes (00) No (99) Prefer not to say / Don't know
Hands.....
Feet.....
Head and Neck.....
Other, specify_____.....

L24 At which age, were you? (99) Prefer not to say / Don't know
Hands.....
Feet.....
Head and Neck.....
Other, specify_____.....

L25 Since you started you sexual life have you ever had Candida Albicans (yeast infection)?
(00) No (GO TO (GO TO L24) (99) Prefer not to say / Don't know (GO TO L24)
(01) Yes

L26 If yes, where? (01) Yes (00) No (99) Prefer not to say / Don't know
Genital.....
Mouth.....
Other, specify_____.....

L27 Have you ever had a sexually transmitted disease?.....
(00) No (GO TO SECTION M) (99) Prefer not to say / Don't know (GO TO SECTION M)
(01) Yes

L28 If yes, which ones? (01) Yes; (00) No; (99) Prefer not to say / Don't know
Gonorrhea .....
Syphillis .....
Herpes .....
Chlamydia .....
AIDS .....

Section L – Marriage, intimacy and life as a couple

0	5			
Country		ID N°		

L29 At which age, were you? (99) Prefer not to say / Don't know

Gonorrhea ……	
Syphillis ……	
Herpes ……	
Chlamydia ……	
AIDS ……	

Section M – Social support | 0 5 Country | ID N°

M. SOCIAL SUPPORT

Finally I would like to ask you some questions about your friends, relatives and the people you live with.

M1 Is there <u>someone in particular</u> in your life that you think would listen to you and give you emotional support if you needed it?..... ☐☐
(01) Yes (00) No

M2 In your life in general, do you think you have enough opportunities to talk openly and share your feelings about things?..... ☐☐
(00) No (01) Yes

M3 In general, do you prefer to keep your feelings to yourself?..... ☐☐
(00) No (01) Yes

M4 Can you remember any life event(s) in your adulthood that have either positively or negatively impacted upon you?..... ☐☐
(00) No (01) Yes

M5 Can you tell me what? (Describe)**(LC)**.....
1_____ ☐☐
2_____ ☐☐
3_____ ☐☐
4_____ ☐☐
5_____ ☐☐

M6 Could you please tell me how much impact did this (se) event (s) have in your life?
(Use Answer Sheet)……..

-4 -3 -2 -1 0 1 2 3 4
Very negative no impact Very positive

Event 1 ……..score: _____…….. ☐☐
Event 2 ……..score: _____…….. ☐☐
Event 3 ……..score: _____…….. ☐☐
Event 4 ……..score: _____…….. ☐☐
Event 5 ……..score: _____…….. ☐☐

M7 10% of participants of this study will be re-interviewed. Do you agree to be re-contacted for you to participate a second time? ☐☐

M8 Incomplete questionnaire?…….. ☐☐
Reason:_____

_____ _____

Section M – Social support | 0 5 Country | ID N°

M9 Time of end of interview..... | Hour - Minute

M10 Data enterer's initials? .....

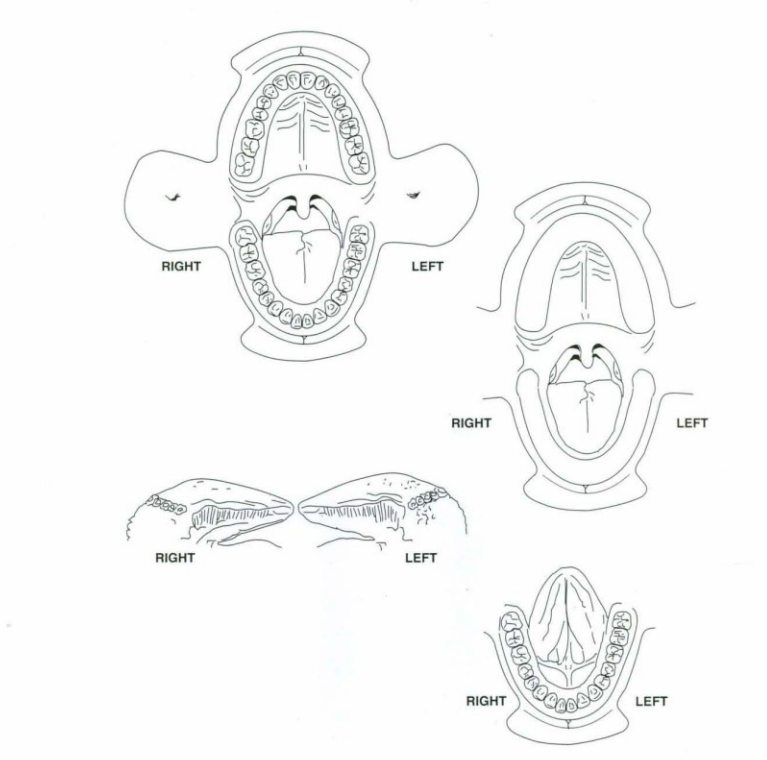
Participant's comments:

Section N – Oral Assessment Form & Biological Sampling | 0 5 Country | ID N°

N. ORAL ASSESSMENT FORM & BIOLOGICAL SAMPLING

N1. VISIBLE LESIONS AND IRRITATIONS

Circle the place in the mouth where you see the lesion.



Section N – Oral Assessment Form & Biological Sampling | 0 5 Country | ID N°

N2 Where is the lesion located?
(01) Oro-pharynx
(02) Tongue (e.g., lateral, posterior, beneath)
(03) Palate
(04) Cheek
(05) Alveol (e.g., buccal, lingual, palatine)
(06) Floor of mouth
(88) NA/ Control

N3 What type of lesion is this?
Please refer to the Interviewer's Guide for thorough definitions
(01) White lesion
(02) Red lesion
(03) Ulcerated lesion
(04) Blistering/ sloughing lesion
(05) Pigmented lesion
(06) Papillary lesion
(07) Soft tissue enlargement
(88) NA/ Control

N4 DECAYING TEETH ASSESSMENT

18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
48	**47**	**46**	**45**	**44**	**43**	**42**	**41**	**31**	**32**	**34**	**34**	**35**	**36**	**37**	**38**

Place the following codes to correspond with each tooth above.

Code 0: Sound Tooth
All surfaces that are present and have no caries experience. A surface is recorded as "sound" if it shows no evidence of treated or untreated dental caries in dentine.

Code 1: Cavities/ Decay
All surfaces that present cavities or decay.

Code 2: Filling
All surfaces that have received any kind of filling.

Code 3: Missing
All the teeth that are missing on the arcade

Section N – Oral Assessment Form & Biological Sampling | 0 5 Country | ID N°

N5 PERIODONTAL STATUS

Please provide a description of the subject's general periodontal status (e.g., gingival colour, alteration of colour in the gingival, loss of attachment, etc.)

Note: this should be done visually without any instrumentation

BIOLOGICAL SAMPLING

N6 Was a mouthwash sample taken?
(01) Yes (00) No

N7 Was a sample for HPV analysis taken?
(this sample is taken from the lesion site for cases, and from healthy buccal cells for controls)
(01) Yes (00) No

N8 Was a sample for genetic analysis taken?
(this sample is taken from healthy buccal cells from both the cases and controls)
(01) Yes (00) No

N9 Were all 3 above samples stored in the HeNCe refrigerator?
(01) Yes (00) No

N10 Please document below if there was any comments from the biological sampling (e.g., occurrence of untoward/adverse events such as patient discomfort, bleeding).

LIFE GRID

Other	Housing	Yr	Age	Education/Jobs	Habits
			5		
			10		
			15		
			20		
			25		
			30		
			35		
			40		
			45		
			50		
			55		
			60		
			65		
			70		
			75		