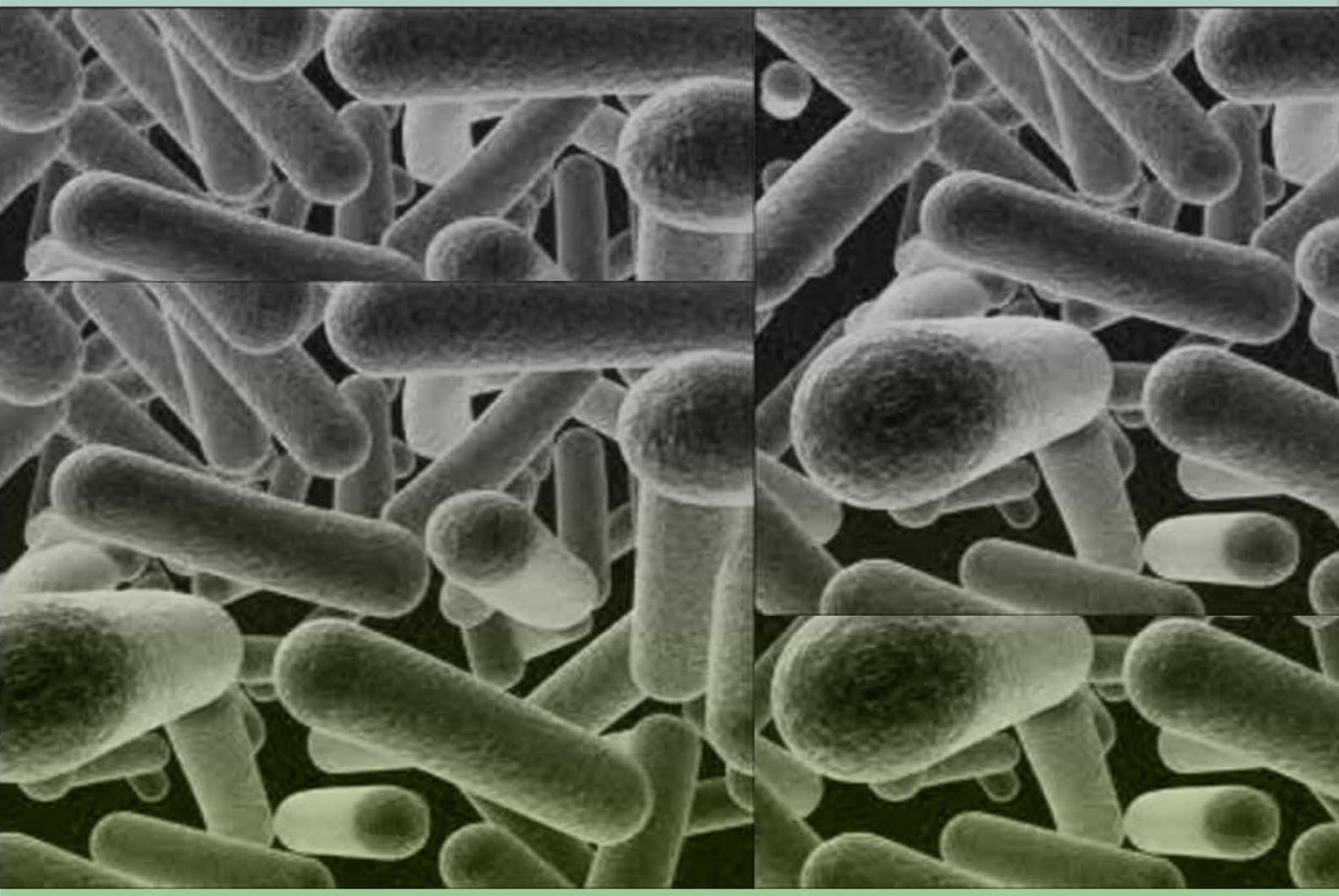
May, 2016 • Volume 1, Issue 1

Openventio PUBLISHERS

ISSN 2473-4780

EPIDEMIOLOGY

Open Journal



www.openventio.org

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780

Open Journal

TABLE OF CONTENTS

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-101

Letter to the Editor

Corresponding author
Scott Lee, MD, MPH, FACS
Lecturer
School of Public Health
University of California
Berkeley, CA, USA
E-mail: selee@stanford.edu

Volume 1 : Issue 1
Article Ref. #: 1000EPOJ1101

Article History
Received: January 8th, 2016
Accepted: January 8th, 2016
Published: January 11th, 2016

Citation
Lee S. Research proposal for medication adherence using smartphone technology. *Epidemiol Open J*. 2016; 1(1): 1. doi: 10.17140/EPOJ-1-101

Research Proposal for Medication Adherence Using Smartphone Technology

Scott Lee, MD, MPH, FACS*

School of Public Health, University of California, Berkeley, CA, USA

The field of medicine has changed dramatically with the advent of Smartphone technology. Patients are able to access their records with a click of the button. Lab results are available online immediately. Technological advances have allowed various gadgets and sensors to track human activity like never before. Epidemiology has advanced to the point where cell phones are used to track disease in remote parts of Sub-Saharan Africa. The one area which has not been studied is the role of the Smartphone in not just tracking disease, but also as an intervention in medication adherence. We are studying specifically the role of the Smartphone in medication adherence with respect to glaucoma. Glaucoma is an insidious disease where patients may not know that they are going blind. It is imperative that they adhere to medication usage by their physician, yet many see the need to. We are looking into using Smartphone technology to increase medication adherence, as well as to track the progression of glaucoma. If you have interest in our research and interested in participating, please contact me at selee@stanford.edu.

Thank you.

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

Research

*Corresponding author
Mangesh S Pednekar, PhD
Director
Healis-Sekhsaria Institute for Public Health
501 Technocity Plot X-4/5 TTC Industrial Area
Mahape, Navi Mumbai
Maharashtra 400 701, India
Tel. 91 22 2778 0924/82/4002 5146
Fax: 91 22 2778 0923
E-mail: pednekarm@healis.org

Volume 1 : Issue 1
Article Ref. #: 1000EPOJ1102

Article History
Received: February 12th, 2016
Accepted: February 29th, 2016
Published: March 7th, 2016

Citation
Pednekar MS, Vasa J, Narake SS, Sinha DN, Gupta PC. Tobacco and Alcohol Associated Mortality among Men by Socio-economic Status in India. *Epidemiol Open J*. 2016; 1(1): 2-15. doi: 10.17140/EPOJ-1-102

Tobacco and Alcohol Associated Mortality among Men by Socio-Economic Status in India

Mangesh S. Pednekar, PhD[1*]; Jooi Vasa, MS[1]; Sameer S. Narake, MS[1]; Dhirendra N. Sinha, MD, PhD[2]; Prakash C. Gupta, DSc[1]

[1]Healis Sekhsaria Institute for Public Health, Mahape, Navi Mumbai, India
[2]School of Preventive Oncology, Patna, India

ABSTRACT

Background: Tobacco use, alcohol use and Socioeconomic status (SES) are all strongly associated with mortality. These risk factors however, are also strongly associated with each other. The effect of the interrelationship between these risk factors on mortality has not been examined in India.
Objectives: To study tobacco and alcohol associated Hazard Ratios (HRs) stratified by SES.
Methods: A cohort of 34,055 men (age>=45 years) was recruited through house visits and information collected through face-to-face interviews during 1994 to 1997. During 1999 to 2003, follow-up through repeat house visits was conducted and deaths were recorded. Education level was used as proxy for SES. Cox proportional hazards model provided HRs and 95% Confidence Intervals (CIs) for tobacco/alcohol associated mortality adjusted for alcohol/tobacco and other confounders. Additionally, HRs was stratified by SES for their individual (tobacco, alcohol use) and their joint effect on mortality.
Results: For tobacco associated mortality, stratification by SES showed higher HRs for high SES bidi smokers (HR=2.01) compared to corresponding low SES bidi smokers (HR=1.41). For alcohol associated mortality, HRs were higher among high SES 'country/desi' drinkers (HR=1.56) compared to corresponding low SES counterpart (HR=1.31). After adjusting for alcohol exposure, the highest attenuation of HRs (>20%) for tobacco associated mortality was observed for deaths from tuberculosis and digestive system diseases (mainly liver diseases) among various forms of tobacco users.
Conclusions: The examination of differences in mortality risks by SES, showing higher HRs among high SES bidi smokers and high SES 'country/desi' drinkers, have implications for public health policies.

KEYWORDS: Alcohol; India; Mortality; Risk ratios; Smokeless tobacco; Smoking; Socioeconomic status.

INTRODUCTION

Globally, tobacco kills approximately 6 million people and causes more than a trillion dollars of economic damage each year.[1] Similarly, the use of alcohol kills approximately 2.3 million people each year. More than half of these deaths occur from NCDs (Non-communicable disease) including cancer, cardiovascular disease, and liver cirrhosis.[2] Nearly, 80% of NCD deaths occur in low-and-middle-income countries (such as India). Tobacco consumption and alcohol use together accounts for about 18% of global deaths.[3] In addition to communicable diseases, NCDs are becoming major threat in India for increasing the burden of diseases. Age standardized NCD death rates (per 100,000 populations) ranges from 571 among women to 782 among men.[2] In addition to cigarette smoking the varying forms of tobacco and alcohol practices prevalent in India contribute to increasing the disease burden.[4-11] The mortality patterns may also vary by Socioeconomic status (SES). The common observed association between SES and health outcomes has been of a strong inverse relationship with those in lower SES

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

groups having higher mortality.[5-9] Thus, examining tobacco and/or alcohol associated mortality by SES may delineate the health disparities that may further help to address the disparities

Using the Mumbai cohort study,[8] we had previously reported tobacco as an independent risk factor for deaths from NCDs and communicable diseases. These earlier results on tobacco associated mortality, based on follow-up of 99,570 men and women (age=>35 year), showed higher Hazard Ratios (HRs) for bidi, cigarette smokers, and smokeless tobacco (SLT) users compared to never-users.[8] These HRs were adjusted for age and education (surrogate for socioeconomic status: referred here after as SES) but not for alcohol use (alcohol consumption information was not available for these 99570 individuals). Alcohol use information however, was available for a subsequent cohort[9-12] of 34,055 men (age=>45 year) and the follow-up results from this cohort[9] showed that alcohol use was associated with excess risk for all-causes mortality [Hazard Ratio (HR) 1.22, 95% Confidence Intervals (CIs) 1.13-1.31, adjusted for age, education, and tobacco use]. Since tobacco use and alcohol consumption were closely associated,[9-10] we now report results on the effect of adjustment of alcohol use on HRs associated with tobacco use. Furthermore, we are extending our findings to examine these associations by socioeconomic differences. Earlier, we had demonstrated the joint effect of tobacco and alcohol use on all-causes mortality.[9] In this paper, we present the joint effect of tobacco (SLT use, bidi, cigarette smoking) and alcohol use on all-causes mortality stratified by SES.

METHODS

This cohort[9-11] of 34,055 men (age=>45 year) was recruited through house-to-house visits and face-to-face interviews in the city of Mumbai during 1994 to 1997. The survey area was restricted to the main city, covering an area of around 70 sq. km. The persons were recruited from voter's list which provided name, age, sex, and address of all individuals 18 years and older. Some individuals not listed on the voters' list were included when they insisted that they were permanent residents (having ration card issued by the government considered as residence proof) of the place. This only formed ~5% of the sample. Additional recruitment detail is published elsewhere.[7] Verbal informed consent was taken from each participant. Data analyses plan was approved from Healis-Sekhsaria Institute for Public Health Institutional Review Board (IRB).

FOLLOW-UP

An active house-to house follow-up was conducted during 1999 to 2003 for recording the participant's vital status. Field investigators were provided with names and addresses of the cohort individuals and were ask to revisit each person. Deaths recorded were then linked with the information obtained from Mumbai (Bombay) Municipal Corporation death registers. The causes of death information were abstracted from the Municipal Corporation death records and an underlying cause of death was assigned and coded as per International Classification of Diseases (ICD Version 10) guidelines. Less than 5% participants were lost-to-follow-up, the most common reason being demolition of their residence for re-development. Additional details regarding the follow-up methodology and estimation of person-years of follow-up have been published previously.[7-16]

MEASURES

Tobacco use was categorized into three categories: (1) never tobacco users (2) ever used SLT and (3) ever smoked tobacco (may include smokers who use smokeless tobacco as well). Smokers were further categorized as cigarette smokers and bidi smokers (may include bidi smokers who also use cigarette or other smoking forms). Information regarding the frequency per day of tobacco use was sub-divided into three groups: 1-5 times, 6-10 times and >10 times per day. Alcohol usage was categorized as never drinkers and ever drinkers. Alcohol ever drinkers were further categorized as country/desi drinker (brewed and distilled locally made using fruits or grains)[9] and any other type drinkers (such as Indian Made Foreign Liquor (IMFL), beer, toddy and spirits not presented due to smaller number in each form). IMFL are distilled and marketed in India, which include whisky, rum, brandy and gin. Frequency of drinking was categorized as those who drank once a month, five or less times a month, three or less times a week (recoded by clubbing these three categories into one referred as less than four times a week), four to five times a week and more than five times a week (recoded by clubbing these two categories into one and referred as four or more times a week).[9]

Socioeconomic status (SES) was defined using education as proxy. It was broadly categorised into two groups: low SES (included education level of illiterate, primary school-up to 5 yrs of education, and middle school-6 to 8 yrs of education) and high SES (included education level of secondary school-9 to 12 yrs of education, and college-above 12 yrs of education).

STATISTICAL ANALYSIS

SPSS Version 13 (IBM, USA) was used for all analysis. The analysis for this study was conducted in 2014. Cox proportional hazards model was used to estimate tobacco associated HRs adjusted for age, education and alcohol consumption, and alcohol associated HRs adjusted for age, education, and tobacco usage status. HRs for tobacco and alcohol associated all-cause and cause-specific mortality were further stratified by SES. HRs for joint effect of tobacco and alcohol consumption stratified by SES were also presented. HRs for joint effect of frequency of tobacco use and frequency of alcohol use by SES were also presented.

RESULTS

Demographics

Table 1 presents demographics of the 34,055 men according to tobacco habit. Around 90% of alcohol users were to-

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

bacco users while around 30% of tobacco users were alcohol users. Cigarette smoking was more common among high SES (2789/4631=64%), while in contrast, SLT use (6473/10169=60%) and bidi smoking (5479/7111=77%) was common among low SES.

SES Differences in Mortality from Use of Tobacco

Referring to Table 2, stratification of HRs by SES for all-cause mortality shows higher HR for high SES bidi smoker (HR=2.01) than low SES bidi smoker (HR=1.41). Additionally, within high SES smokers, HR for bidi smokers (2.01) was higher than cigarette smokers (1.28), while within low SES smoker the HRs were similar (1.40) for bidi and cigarette smokers. Bidi smoking increased the risk of mortality from respiratory diseases, TB, and neoplasm among smokers from both high as well as low SES, while cigarette smoking increased risk of mortality from neoplasms. SLT use increased the risk of mortality from respiratory diseases and neoplasms (only high SES), and TB (only low SES).

		Non user	Smokeless	Only Cigarette	Bidi[+]
		N=12144	N=10169	N=4631	N=7111
Age group	45-49	5111	3912	1721	2615
	50-54	1980	2047	863	1451
	55-59	1435	1399	633	860
	60-64	1325	1119	578	949
	65-69	929	786	393	578
	70-74	720	475	257	378
	75-79	333	244	118	153
	80-84	182	117	48	90
	85+	129	70	20	37
Alcohol	Never	11013	7179	2924	4516
	Ever	1131	2990	1707	2595
Education level	Higher	6377	3696	2789	1632
	Lower	5767	6473	1842	5479

[+]=may include bidi plus mixed (bidi and cigarette) smokers

Table 1: Sample characteristics of 34,055 men.

	Never Tobacco User	Smokeless Tobacco User[b]	Smoker[c]	
Cause of Death[a]			**Only Cigarette**	**Bidi[d]**
All-causes				
Person year	55648	45608	21126	30449
Deaths(n=)	1074	1046	550	915
HR[e](95% CI)	1	1.22(1.12, 1.33)	1.41(1.27, 1.57)	1.61(1.47, 1.76)
HR[f](95% CI)	1	1.18(1.08, 1.28)	1.33(1.20, 1.48)	1.52(1.38, 1.67)
Percent change in HR		3.28	5.67	5.29
High SES[g]				
Person year	31040	17922	12923	7388
Deaths(n=)	541	325	268	208
HR[h](95% CI)	1	1.20(1.05, 1.38)	1.32(1.14, 1.53)	2.08(1.77, 2.44)
HR[i](95% CI)	1	1.18(1.03, 1.36)	1.28(1.10, 1.48)	2.01(1.71, 2.37)
Percent change in HR		1.67	3.03	3.37
Low SES[g]				
Person year	24607	27686	8203	23060
Deaths(n=)	533	721	282	707

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

HR[h](95% CI)	1	1.27(1.13, 1.42)	1.49(1.29, 1.73)	1.51(1.35, 1.69)
HR[i](95% CI)	1	1.21(1.08, 1.35)	1.40(1.21, 1.62)	1.41(1.26, 1.59)
Percent change in HR		4.72	6.04	6.62
Respiratory system diseases [J00-J99]				
Deaths(n=)	70	76	38	103
HR[e](95% CI)	1	1.40(1.01,1.95)	1.63(1.10, 2.43)	2.86(2.09, 3.93)
HR[f](95% CI)	1	1.32(0.95,1.84)	1.49(1.00, 2.23)	2.62(1.89, 3.64)
Percent change in HR		5.71	8.59	8.39
Pneumonia [J18]				
Deaths(n=)	12	20	4	21
HR[e](95% CI)	1	2.44(1.18, 5.04)	1.08(0.35, 3.35)	4.51(2.14, 9.53)
HR[f](95% CI)	1	2.33(1.12, 4.86)	1.00(0.32, 3.15)	4.19(1.95, 9.01)
Percent change in HR		4.51	7.41	7.10
COPD [J42-J46]				
Deaths(n=)	48	51	30	74
HR[e](95% CI)	1	1.31(0.88, 1.95)	1.84(1.16, 2.91)	2.73(1.87, 3.98)
HR[f](95% CI)	1	1.24(0.83, 1.85)	1.71(1.07, 2.72)	2.53(1.72, 3.73)
Percent change in HR		5.34	7.07	7.33
Respiratory system diseases [J00-J99]				
High SES[g]				
Deaths(n=)	33	27	17	17
HR[h](95% CI)	1	1.78(1.07, 2.97)	1.47(0.82, 2.64)	3.20(1.77, 5.78)
HR[i](95% CI)	1	1.76(1.05, 2.94)	1.41(0.77, 2.58)	3.10(1.70, 5.66)
Percent change in HR		1.12	4.08	3.13
Low SES[g]				
Deaths(n=)	37	49	21	86
HR[h](95% CI)	1	1.36(0.89, 2.09)	1.68(0.98, 2.88)	2.83(1.92, 4.18)
HR[i](95% CI)	1	1.24(0.80, 1.92)	1.51(0.87, 2.61)	2.53(1.70, 3.78)
Percent change in HR		8.82	10.12	10.60
TB [A15-A19]				
Deaths(n=)	40	64	25	63
HR[e](95% CI)	1	1.94(1.30, 2.90)	1.74(1.05, 2.87)	2.95(1.96, 4.45)
HR[f](95% CI)	1	1.54(1.03, 2.33)	1.27(0.76, 2.13)	2.19(1.43, 3.35)
Percent change in HR		20.62	27.01	25.76
High SES[g]				
Deaths(n=)	22	18	13	23
HR[h](95% CI)	1	1.42(0.76, 2.65)	1.43(0.72, 2.84)	4.49(2.49, 8.10)
HR[i](95% CI)	1	1.16(0.61, 2.19)	1.02(0.50, 2.06)	3.31(1.79, 6.09)
Percent change in HR		18.31	28.67	26.28
Low SES[g]				
Deaths(n=)	18	46	12	40
HR[h](95% CI)	1	2.37(1.37, 4.10)	1.95(0.94, 4.07)	2.46(1.41, 4.31)

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

HR[i](95% CI)	1	1.89(1.08, 3.31)	1.50(0.71, 3.17)	1.88(1.06, 3.36)
Percent change in HR		20.25	23.08	23.58
Neoplasms [C00-C97]				
Deaths(n=)	39	53	45	66
HR[e](95% CI)	1	1.88(1.24, 2.86)	3.03(1.97, 4.66)	3.66(2.42, 5.54)
HR[f](95% CI)	1	1.83(1.20, 2.79)	2.90(1.87, 4.50)	3.51(2.30, 5.36)
Percent change in HR		2.66	4.29	4.10
Oral and pharynx neoplasms [C00-C14]				
Deaths(n=)	1	3	3	11
HR[e](95% CI)	1	3.63(0.37, 35.50)	7.89(0.82, 76.07)	22.42(2.71, 185.29)
HR[f](95% CI)	1	3.23(0.33, 31.98)	6.62(0.67, 65.20)	19.46(2.31, 163.95)
Percent change in HR		11.02	16.10	13.20
Respiratory neoplasms [C30-C39]				
Deaths(n=)	3	8	8	16
HR[e](95% CI)	1	3.26(0.86, 12.41)	6.84(1.81, 25.90)	10.35(2.93, 36.56)
HR[f](95% CI)	1	2.99(0.78, 11.49)	6.06(1.57, 23.37)	9.23(2.57, 33.14)
Percent change in HR		8.28	11.40	10.82
Neoplasms [C00-C97]				
High SES[g]				
Deaths(n=)	18	19	23	19
HR[h](95% CI)	1	2.25(1.18, 4.30)	3.50(1.88, 6.49)	6.37(3.33, 12.21)
HR[i](95% CI)	1	2.26(1.18, 4.33)	3.53(1.88, 6.65)	6.43(3.32, 12.45)
Percent change in HR		-0.44	-0.86	-0.94
Low SES[g]				
Deaths(n=)	21	34	22	47
HR[h](95% CI)	1	1.55(0.90, 2.68)	2.79(1.53, 5.08)	2.50(1.49, 4.19)
HR[i](95% CI)	1	1.45(0.83, 2.53)	2.57(1.40, 4.74)	2.31(1.36, 3.92)
Percent change in HR		6.45	7.89	7.60
Circulatory system diseases [I00-I99]				
Deaths(n=)	367	291	164	205
HR[e](95% CI)	1	1.09(0.94, 1.28)	1.26(1.05, 1.52)	1.24(1.04, 1.49)
HR[f](95% CI)	1	1.07(0.91, 1.25)	1.22(1.01, 1.48)	1.20(1.00, 1.44)
Percent change in HR		1.83	3.17	3.23
High SES[g]				
Deaths(n=)	199	114	83	53
HR[h](95% CI)	1	1.18(0.94, 1.49)	1.17(0.90, 1.51)	1.59(1.17, 2.16)
HR[i](95% CI)	1	1.19(0.94, 1.50)	1.19(0.91, 1.55)	1.61(1.18, 2.19)
Percent change in HR		-0.85	-1.71	-1.26
Low SES[g]				
Deaths(n=)	168	177	81	152
HR[h](95% CI)	1	1.06(0.85, 1.31)	1.38(1.06, 1.81)	1.10(0.88, 1.38)
HR[i](95% CI)	1	1.00(0.80, 1.24)	1.30(0.99, 1.70)	1.03(0.82, 1.30)

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

Percent change in HR		5.66	5.80	6.36
Digestive system diseases [K00-93]				
Deaths(n=)	28	30	15	25
HR[e](95% CI)	1	1.41(0.84, 2.38)	1.41(0.75, 2.65)	2.04(1.16, 3.59)
HR[f](95% CI)	1	1.07(0.63, 1.84)	0.96(0.50, 1.84)	1.43(0.80, 2.57)
Percent change in HR		24.11	31.91	29.90
Liver [K70-77]				
Deaths(n=)	21	22	14	23
HR[e](95% CI)	1	1.34(0.73, 2.46)	1.75(0.89, 3.45)	2.43(1.31, 4.50)
HR[f](95% CI)	1	0.99(0.53, 1.84)	1.14(0.56, 2.30)	1.64(0.86, 3.11)
Percent change in HR		26.12	34.86	32.51
Digestive system diseases [K00-93]				
High SES[g]				
Deaths(n=)	21	15	7	6
HR[h](95% CI)	1	1.27(0.65, 2.47)	0.81(0.35, 1.92)	1.33(0.54, 3.32)
HR[i](95% CI)	1	1.00(0.51, 1.99)	0.55(0.23, 1.33)	0.95(0.37, 2.41)
Percent change in HR		21.26	32.10	28.57
Low SES[g]				
Deaths(n=)	7	15	8	19
HR[h](95% CI)	1	2.00(0.81, 4.92)	3.49(1.26, 9.68)	3.18(1.33, 7.60)
HR[i](95% CI)	1	1.47(0.58, 3.69)	2.41(0.84, 6.87)	2.19(0.89, 5.41)
Percent change in HR		26.50	30.95	31.13
Others				
Deaths(n=)	530	532	263	453
HR[e](95% CI)	1	1.22(1.08, 1.38)	1.40(1.20, 1.62)	1.51(1.33, 1.72)
HR[f](95% CI)	1	1.20(1.06, 1.35)	1.36(1.16, 1.58)	1.47(1.28, 1.68)
Percent change in HR		1.64	2.86	2.65
High SES[g]				
Deaths(n=)	248	132	125	90
HR[h](95% CI)	1	1.08(0.87, 1.33)	1.35(1.09, 1.67)	1.99(1.56, 2.54)
HR[i](95% CI)	1	1.07(0.87, 1.33)	1.34(1.07, 1.67)	1.97(1.54, 2.53)
Percent change in HR		0.93	0.74	1.01
Low SES[g]				
Deaths(n=)	282	400	138	363
HR[h](95% CI)	1	1.32(1.13, 1.54)	1.41(1.15, 1.73)	1.46(1.25, 1.71)
HR[i](95% CI)	1	1.29(1.10, 1.50)	1.36(1.11, 1.68)	1.42(1.21, 1.66)
Percent change in HR		2.27	3.55	2.74

[a]=Coded as per ICD 10
[b]=only non-smoker
[c]=may include smokers plus mixed (smoking and smokeless tobacco) users
[d]=may include bidi plus mixed (bidi and cigarette) smokers
[e]=age and education adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by using Cox regression model
[f]=age, education and alcohol adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by using Cox regression model
[g]=low SES (those reporting education below high school) and high SES (those reporting education high school or above)
[h]=age adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by using Cox regression model
[i]=age and alcohol adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by using Cox regression model

Table 2: Hazard Ratios in tobacco users for deaths reported among 34,055 men.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

SES Differences in Mortality from Use of Alcohol

Referring to Table 3, stratification of HRs by SES for all-cause mortality shows higher HRs for both high (1.56) and low (1.31) SES country/desi drinkers compared to any other type drinkers. Country/desi drinking increased the risk of mortality from respiratory diseases, TB, and digestive diseases for both high as well as low SES drinkers.

Table 4 shows joint effect of tobacco and alcohol use stratified by SES. Exclusive drinking was associated with excess mortality among low SES drinkers. Similarly, exclusive SLT use was associated with excess mortality among low SES users. While, exclusive cigarette and exclusive bidi smoking were associated with excess mortality among both low as well as high SES smokers. The HRs were higher among those who drank and used tobacco compared to those who only drank or only used tobacco.

Table 5 shows the joint effect of frequency of tobacco and frequency of alcohol use stratified by SES.

Attenuation of Tobacco Hazard Ratios

Table 2 also shows the attenuation of tobacco associated HRs after adjusting for alcohol use. Among smokers and SLT users, the attenuation in HRs was highest (>20%) for deaths from digestive system diseases; mainly driven by deaths from liver diseases and for deaths from tuberculosis (TB). The next highest attenuation in HRs ranged between 10% to 20% for

		Ever Alcohol user	
Cause of Death[a]	**Never Alcohol User**	**Any type**	**Country/desi liquor**
All			
Person year	114459	38372	25819
Deaths	2556	1029	746
HR[b](95% CI)	1	1.34(1.25, 1.44)	1.50(1.38, 1.63)
HR[c](95% CI)	1	1.23(1.14, 1.33)	1.37(1.26, 1.49)
Percent change in HR		8.21	8.67
High SES			
Person year	52933	16341	7731
Deaths	999	343	193
HR[d](95% CI)	1	1.26(1.11, 1.43)	1.77(1.51, 2.06)
HR[e](95% CI)	1	1.12(0.99, 1.28)	1.56(1.33, 1.84)
Percent change in HR		11.11	11.86
Low SES			
Person year	61526	22031	18087
Deaths	1557	686	553
HR[d](95% CI)	1	1.36(1.24, 1.49)	1.42(1.29, 1.56)
HR[e](95% CI)	1	1.26(1.15, 1.38)	1.31(1.19, 1.45)
Percent change in HR		7.35	7.15
Disease of respiratory [J00-J99]			
Deaths	198	89	69
HR[b](95% CI)	1	1.66(1.29, 2.14)	2.00(1.51, 2.65)
HR[c](95% CI)	1	1.39(1.07, 1.81)	1.68(1.26, 2.24)
Percent change in HR		16.27	16.00
High SES			
Deaths	70	24	15
HR[d](95% CI)	1	1.35(0.85, 2.15)	2.38(1.35, 4.21)
HR[e](95% CI)	1	1.13(0.70, 1.84)	1.91(1.06, 3.45)
Percent change in HR		16.3	19.75

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

Low SES			
Deaths	128	65	54
HR[d](95% CI)	1	1.75(1.30, 2.37)	1.96(1.42, 2.70)
HR[e](95% CI)	1	1.48(1.08, 2.02)	1.66(1.19, 2.31)
Percent change in HR		15.43	15.31
TB [A15-A19]			
Deaths	100	92	81
HR[b](95% CI)	1	2.95(2.21, 3.92)	3.91(2.89, 5.28)
HR[c](95% CI)	1	2.56(1.90, 3.45)	3.38(2.47, 4.63)
Percent change in HR		13.22	13.55
High SES			
Deaths	38	38	32
HR[d](95% CI)	1	3.16(2.01, 4.96)	5.78(3.59, 9.30)
HR[e](95% CI)	1	2.71(1.69, 4.35)	5.03(3.02, 8.38)
Percent change in HR		14.24	12.98
Low SES			
Deaths	62	54	49
HR[d](95% CI)	1	2.62(1.82, 3.79)	3.04(2.08, 4.45)
HR[e](95% CI)	1	2.29(1.56, 3.35)	2.64(1.78, 3.91)
Percent change in HR		12.6	13.16
Neoplasms [C00-C97]			
Deaths	141	62	41
HR[b](95% CI)	1	1.51(1.12, 2.05)	1.65(1.15, 2.36)
HR[c](95% CI)	1	1.18(0.86, 1.60)	1.28(0.89, 1.84)
Percent change in HR		21.85	22.42
High SES			
Deaths	58	21	11
HR[d](95% CI)	1	1.39(0.84, 2.30)	1.90(0.99, 3.66)
HR[e](95% CI)	1	0.95(0.57, 1.59)	1.24(0.64, 2.42)
Percent change in HR		31.65	34.74
Low SES			
Deaths	83	41	30
HR[d](95% CI)	1	1.58(1.08, 2.30)	1.53(1.01, 2.34)
HR[e](95% CI)	1	1.33(0.91, 1.96)	1.30(0.84, 2.00)
Percent change in HR		15.82	15.03
Disease of circulatory [I00-I99]			
Deaths	772	255	156
HR[b](95% CI)	1	1.19(1.03, 1.38)	1.22(1.02, 1.45)
HR[c](95% CI)	1	1.14(0.98, 1.32)	1.16(0.97, 1.40)
Percent change in HR		4.20	4.92
High SES			
Deaths	356	93	39

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

HR[d](95% CI)	1	1.01(0.80, 1.27)	1.13(0.81, 1.58)
HR[e](95% CI)	1	0.94(0.74, 1.19)	1.03(0.73, 1.45)
Percent change in HR		6.93	8.85
Low SES			
Deaths	416	162	117
HR[d](95% CI)	1	1.30(1.08, 1.56)	1.26(1.02, 1.55)
HR[e](95% CI)	1	1.27(1.05, 1.54)	1.23(0.99, 1.53)
Percent change in HR		2.31	2.38
Digestive [K00-93]			
Deaths	49	49	37
HR[b](95% CI)	1	3.21(2.15, 4.78)	4.01(2.58, 6.23)
HR[c](95% CI)	1	3.07(2.02, 4.68)	3.86(2.42, 6.15)
Percent change in HR		4.36	3.74
High SES			
Deaths	26	23	15
HR[d](95% CI)	1	2.90(1.65, 5.09)	4.31(2.26, 8.21)
HR[e](95% CI)	1	3.16(1.74, 5.71)	4.85(2.43, 9.68)
Percent change in HR		-8.97	-12.53
Low SES			
Deaths	23	26	22
HR[d](95% CI)	1	3.48(1.97, 6.13)	3.73(2.06, 6.76)
HR[e](95% CI)	1	2.94(1.63, 5.30)	3.16(1.70, 5.84)
Percent change in HR		15.52	15.28
Others			
Deaths	1296	482	362
HR[b](95% CI)	1	1.21(1.09, 1.35)	1.35(1.20, 1.52)
HR[c](95% CI)	1	1.11(1.00, 1.24)	1.24(1.10, 1.40)
Percent change in HR		8.26	8.15
High SES			
Deaths	451	144	81
HR[d](95% CI)	1	1.16(0.96, 1.40)	1.61(1.26, 2.04)
HR[e](95% CI)	1	1.03(0.85, 1.25)	1.43(1.12, 1.84)
Percent change in HR		11.21	11.18
Low SES			
Deaths	845	338	281
HR[d](95% CI)	1	1.22(1.07, 1.38)	1.29(1.13, 1.48)
HR[e](95% CI)	1	1.13(0.99, 1.28)	1.19(1.03, 1.37)
Percent change in HR		7.38	7.75

[a]=Coded as per ICD 10
[b]=age and education adjusted hazard ratios (HRs) and confidence intervals (CIs) by using Cox model.
[c]=age, education and tobacco adjusted hazard ratios (HRs) and confidence intervals (CIs) by using Cox model
[d]= age adjusted hazard ratios (HRs) and confidence intervals (CIs) by using Cox model.
[e]=age and tobacco adjusted hazard ratios (HRs) and confidence intervals (CIs) by using Cox model

Table 3: Number of deaths and hazard ratios by cause of death and alcohol use among 34,055 men.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

	HRs (95% CIs)[e]			
	Tobacco use			
			Smoker[c]	
Alcohol use	Never	Smokeless[b]	Only cigarette	Bidi[d]
Never	1	1.15(1.04, 1.26)	1.36(1.20, 1.54)	1.43(1.29, 1.60)
Person year	50081	32111	13061	19206
Deaths(n=)	975	714	338	529
Ever	1.03(0.84, 1.27)	1.46(1.28, 1.65)	1.52(1.31, 1.77)	1.96(1.74, 2.21)
Person year	5567	13497	8066	11242
Deaths(n=)	99	332	212	386
	HRs(95% CIs)[h]			
High SES[g]				
Never	1	0.98(0.83, 1.15)	1.31(1.10, 1.57)	1.63(1.33, 1.99)
Person year	27491	12937	7845	4659
Deaths(n=)	494	220	166	119
Ever	0.81(0.60, 1.10)	1.51(1.22, 1.87)	1.34(1.08, 1.66)	2.25(1.79, 2.83)
Person year	3549	4985	5078	2729
Deaths(n=)	47	105	102	89
Low SES[g]				
Never	1	1.26(1.11, 1.43)	1.39(1.16, 1.65)	1.41(1.23, 1.61)
Person year	22590	19174	5215	14547
Deaths(n=)	481	494	172	410
Ever	1.35(1.01, 1.80)	1.44(1.23, 1.69)	1.72(1.39, 2.11)	1.91(1.65, 2.21)
Person year	2018	8512	2988	8513
Deaths(n=)	52	227	110	297

b=only non-smoker
c=may include smokers plus mixed (smoking and smokeless tobacco) users
d=may include bidi plus mixed (bidi and cigarette) smokers
e=age and education adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by using Cox regression model
g=low SES (those reporting education below high school) and high SES (those reporting education high school or above)
h=age adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by using Cox regression model

Table 4: Hazard Ratios in tobacco and alcohol users for deaths among 34,055 men.

deaths from oral pharynx and respiratory neoplasm.

DISCUSSION

It is well known in India (and in Mumbai) that bidi smoking is more prevalent among individuals in low SES and cigarette smoking among high SES.[4-7] The HRs in this study however, were higher among high SES bidi smokers and low SES cigarette smokers than their corresponding SES counterpart. Similarly, country/desi drinking was more prevalent in this study among individuals in low SES but higher HRs were observed among high SES country/desi drinkers. This contrasting association of SES with risk factors (tobacco and alcohol use) in terms of prevalence and in terms of mortality risk needs additional cohort studies from other locations.

A general perspective is that risky behaviors such as smoking and alcohol consumption are more prevalent in lower SES groups, therefore population attributable risks are expected to be higher in low SES groups.[17] At present, a lot of research exists for explaining socioeconomic differences for tobacco use within India[4-5,18-19] including Mumbai[6-7] with higher prevalence of smoking and smokeless forms among lower SES groups. However, SES differences for mortality is minimally explored

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

	Alcohol use frequency		
	Never user	<4 times a week	>=4 times a week
Never user	1	0.94(0.70, 1.25)	1.16(0.87, 1.54)
Smokeless[b]			
Frequency per day			
1 to 5	1.16(1.03, 1.30)	1.12(0.85, 1.47)	1.84(1.55, 2.19)
6 to 10	1.08(0.91, 1.29)	1.18(0.80, 1.75)	1.31(0.96, 1.81)
>10	1.18(0.91, 1.54)	0.99(0.49, 1.99)	1.92(1.35, 2.72)
Smoker[c]			
Only cigarette			
Frequency per day			
1 to 5	1.28(1.04, 1.56)	0.75(0.45, 1.26)	1.52(1.11, 2.07)
6 to 10	1.39(1.14, 1.69)	1.30(0.85, 1.98)	1.55(1.12, 2.13)
>10	1.41(1.17, 1.70)	1.63(1.15, 2.33)	2.04(1.58, 2.63)
Bidi[d]			
Frequency per day			
1 to 5	1.25(0.99, 1.58)	1.03(0.57, 1.88)	1.94(1.37, 2.73)
6 to 10	1.46(1.19, 1.79)	1.67(1.17, 2.40)	2.16(1.61, 2.90)
>10	1.55(1.36, 1.76)	1.54(1.17, 2.02)	2.40(2.06, 2.80)
High SES[g]			
Never user	1	0.75(0.51, 1.09)	0.80(0.50, 1.28)
Smokeless[b]			
Frequency per day			
1 to 5	1.04(0.85, 1.27)	1.48(0.99, 2.20)	2.04(1.48, 2.82)
6 to 10	1.07(0.79, 1.46)	1.41(0.73, 2.72)	1.26(0.63, 2.54)
>10	1.12(0.69, 1.82)	0.55(0.14, 2.20)	3.81(2.03, 7.16)
Smoker[c]			
Only cigarette			
Frequency per day			
1 to 5	1.24(0.93, 1.64)	0.37(0.15, 0.90)	1.36(0.84, 2.22)
6 to 10	1.06(0.78, 1.44)	0.99(0.54, 1.80)	1.21(0.73, 2.03)
>10	1.58(1.22, 2.03)	1.42(0.91, 2.22)	2.00(1.41, 2.84)
Bidi[d]			
Frequency per day			
1 to 5	1.60(1.02, 2.51)	1.47(0.55, 3.94)	2.58(1.33, 5.00)
6 to 10	1.04(0.62, 1.73)	2.29(1.08, 4.83)	1.98(1.02, 3.83)
>10	2.13(1.69, 2.69)	2.18(1.32, 3.59)	2.71(1.99, 3.70)
Low SES[g]			
Never user	1	1.23(0.78, 1.95)	1.52(1.07, 2.17)
Smokeless[b]			
Frequency per day			
1 to 5	1.28(1.11, 1.48)	0.95(0.65, 1.38)	1.84(1.49, 2.27)
6 to 10	1.13(0.91, 1.40)	1.09(0.67, 1.77)	1.36(0.95, 1.95)
>10	1.20(0.88, 1.65)	1.30(0.58, 2.91)	1.61(1.06, 2.45)
Smoker[c]			
Only cigarette			

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

Frequency per day 1 to 5	1.28(0.96, 1.70)	1.46(0.78, 2.73)	1.65(1.09, 2.49)
6 to 10	1.75(1.34, 2.28)	1.65(0.91, 3.01)	1.88(1.24, 2.84)
>10	1.24(0.94, 1.64)	1.83(1.03, 3.25)	1.98(1.36, 2.89)
Bidi[d]			
Frequency per day 1 to 5	1.13(0.85, 1.49)	0.87(0.41, 1.84)	1.73(1.16, 2.59)
6 to 10	1.57(1.25, 1.98)	1.47(0.97, 2.22)	2.22(1.59, 3.09)
>10	1.40(1.21, 1.63)	1.32(0.96, 1.83)	2.27(1.90, 2.72)

b=only non-smoker
c=may include smokers plus mixed (smoking and smokeless tobacco) users
d=may include bidi plus mixed (bidi and cigarette) smokers
e=age and education adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by using Cox regression model
g=low SES (those reporting education below high school) and high SES (those reporting education high school or above)
h=age adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by using Cox regression model

Table 5: Hazard Ratios and 95% confidence intervals for frequency of tobacco and frequency of alcohol use for deaths among 34,055 men.

with only one study showing cancer mortality being higher among men with no formal education adjusting for ever-chewing of tobacco.[20] The higher HRs observed in this study for high SES 'country/desi' drinkers counters study findings from other countries showing individuals of lower educational status having higher alcohol-attributable mortality compared to those with higher education.[21-23] Thus the higher HRs among high SES bidi smokers and high SES 'country/desi' drinkers, deviates from widespread notion that higher risks or mortality are seen among lower SES groups,[12-13,15-17] requires further examination. Given these examples, though this data is limited to one study area and does not provide a complete socioeconomic picture of India, the results pose importance of examining for socioeconomic differences. Additionally, findings from this study reiterate the need for further research into risks and mortality outcomes for bidi smokers.

Although, this study shows the increase in the risk of all-cause mortality due to tobacco use (in smoking or SLT form) was attenuated minimally after adjusting for alcohol use. For alcohol associated diseases, such as TB and digestive system diseases (mainly liver diseases) the attenuation was over 20% among SLT users, cigarette and bidi smokers.

The attenuation in the excess risk of mortality for liver diseases among smokers (mainly bidi smokers) and SLT users is consistent with the well-established finding of alcohol intake affecting the liver. However, it may be pointed out that the smoking association with liver diseases [OR=1.6, 95% CI (1.4–1.9)] remained unchanged even after adjusting for alcohol use in a nationally representative case-control study from India.[24] However, these results were neither stratified nor adjusted for SLT use and the liver disease category included causes such as cirrhosis, hepatitis, jaundice, ascites, alcoholism, and alcohol poisoning. So there are few inconsistencies within and between countries but the IARC evaluated the evidence for relationship between smoking and liver cancer and found to be sufficient after adjusting for potential confounders.[25]

The high risk of all-cause and various specific causes of mortality after adjustment for alcohol consumption among smokers observed in this study is consistent with findings from other studies within India[24,26] and a study from China.[27] Higher HRs among bidi smokers than cigarette smokers for all-cause and for specific causes of death reconfirm bidi smoking being as harmful as cigarette smoking.[8,28] This finding has important public health implication in India because about 90% of alcohol drinkers are tobacco users (Table 1) and 66% of smokers are bidi smokers.[4] These results suggest for giving similar priority to bidi smoking and its health effects in addition to cigarette smoking. This current study also supports the conclusion made by Thun et al[29] that after adjusting for age, further adjustment for behavioral and socioeconomic differences between smokers and non-smokers minimally affects the risk estimates associated with smoking.

For SLT users, the high risk of all-cause mortality after adjusting for alcohol use observed in this study is consistent with findings reported from two cohorts from USA[30] but is little different from Trivandrum (India) cohort fndings.[26] For specific causes, such as cancer, the increase in risk observed in our study was similar to other studies within India[26] and outside India.[30] While, for most other causes (such as respiratory, circulatory and digestive system diseases) our findings were little different.[30] Additionally, inconsistencies were also reported for SLT use between cohorts within country. These inconsistent associations of SLT use with all-causes and various specific causes within and between countries probably point out towards more complex nature of SLT products used in different countries and their systemic effect. To further delineate alcohol adjusted SLT and mortality association, there is a need for undertaking multicentre prospective studies in countries where SLT and alcohol use are prevalent.

There are a few limitations with this study. The sample is not representative of the population as individuals residing in upper-middle-class and upper-class housing were excluded. This exclusion was purposive due to reasons of it being difficult to approach because of security constraints and lack of cooperation from the individuals. Hence, these results may not apply to this division of society. This may partially explain the results that we

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

are seeing with this study. Stratifying the analysis by socioeconomic status, namely education, as high education and low education, the high SES individuals in this sample are different from the affluent group (upper-middle-class and upper-class). These high SES individuals may still have lower education and lower income compared to those affluent individuals and therefore we observe such findings from this study of higher HRs among high SES bidi smokers and high SES country/desi drinkers. Additionally, these high SES individuals might have some competing risk factors which is not known and not measured which possibly needs to be further explored. In relation to this, this study is limited to city of Mumbai, thus the results may be varied in other cities or areas within India, for which further research is necessary. Finally, this study reports results only for men. Although women in India do not smoke very much (~3%) but they do report the use of SLT (~18%). However, alcohol drinking among women is not expected to be major confounder for tobacco associated mortality because the prevalence of alcohol use among women in India is rather low (~2%).[31]

CONCLUSION

This study demonstrates the prominent role of SES in explaining mortality differences for risks from bidi smoking and 'country/desi' drinking for which multicentre additional studies are required. In addition to focusing on smoking forms of tobacco use, our study findings highlight the importance of estimating alcohol adjusted risk estimates for SLT users. Furthermore, the findings underscore the important role of alcohol use in tobacco associated mortality for causes such as TB and digestive diseases (mainly liver diseases).

ACKNOWLEDGEMENTS

Authors acknowledge the technical support from the South East Asia Office of the World Health Organisation. The authors also wish to acknowledge the co-operation of the Municipal Corporation of Greater Mumbai (BMC) in providing access to cause of death information and would also like to thank the entire field and study team for their valuable contribution to the study.

AUTHOR'S CONTRIBUTION

Conceived and designed experiment: MSP. Analysed the data: MSP, PCG, SSN. Wrote the paper: MSP, PCG, DNS, JV. Supervised the field work: MSP. Oversaw the data management, the statistical procedures and tests: MSP. Interpreted the results: MSP, PCG, DNS, SSN. Conducted the literature search and interacted with co-authors in subsequent drafts of the paper: MSP, JV.

CONFLICTS OF INTEREST

We do not have any conflict of interest.

REFERENCES

1. World Health Organization. WHO report on the global tobacco epidemic 2013: enforcing bans on tobacco advertising, promotion, and sponsorship. http://apps.who.int/iris/bitstream/10665/85380/1/9789241505871_eng.pdf. Published 2013. Accessed February 10, 2016.

2. World Health Organization. Global status report on noncommunicable diseases 2010. http://www.who.int/nmh/publications/ncd_report_full_en.pdf. Published 2010. Accessed February 10, 2016.

3. Institute for Health Metrics and Evaluation. The Global Burden of Disease: Generating Evidence, Guiding Policy. Seattle, WA, USA. http://www.healthdata.org/sites/default/files/files/data_for_download/2013/WorldBank_SubSaharanAfrica/IHME_GBD_WorldBank_SubSaharanAfrica_FullReport.pdf. Published 2010. Accessed February 10, 2016.

4. Ministry of Health and Family Welfare, Government of India. Global Adult Tobacco Survey - India, 2009-2010. India: MOHFW, Mumbai. Web site. http://mohfw.nic.in/WriteReadData/l892s/1455618937GATS%20India.pdf. Published 2010. Accessed February 10, 2016.

5. Prabhakar B, Narake SS, Pednekar MS. Social disparities in tobacco use in India: the roles of occupation, education and gender. *Indian J Cancer.* 2012; 49(4): 401-409. doi: 10.4103/0019-509X.107747

6. Sorensen G, Gupta PC, Pednekar MS. Social disparities in tobacco use in Mumbai, India: the roles of occupation, education and gender. *Am J Public Health.* 2005; 95(6): 1003-1008. doi: 10.2105/AJPH.2004.045039

7. Gupta PC. Survey of sociodemographic characteristics of tobacco use among 99 598 individuals in Bombay, India using handheld computers. *Tob Control.* 1996; 5(2): 114-120.

8. Gupta PC, Pednekar MS, Parkin DM, Sankaranarayanan R. Tobacco associated mortality in Mumbai (Bombay) India. Results of the Bombay Cohort Study. *Int J Epidemiol.* 2005; 34(6): 1395-1402. doi: 10.1093/ije/dyi196

9. Pednekar MS, Sansone G, Gupta PC. Association of alcohol, alcohol and tobacco with mortality: findings from a prospective cohort study in Mumbai (Bombay), India. *Alcohol.* 2012; 46(2): 139-146. doi: 10.1016/j.alcohol.2011.08.006

10. Gupta PC, Maulik PK, Pednekar MS, Saxena S. Concurrent alcohol and tobacco use among a middle-aged and elderly population in Mumbai. *Natl Med J India.* 2005; 18(2): 88-91.

11. Gupta PC, Saxena S, Pednekar MS, Maulik PB. Alcohol consumption among middle aged and elderly men: A community

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-102

study from Western India. *Alcohol Alcohol.* 2003; 38(4): 327-331. doi: 10.1093/alcalc/agg077

12. Adler NE, Boyce T, Chesney MA, et al. Socioeconomic status and health, the challenge of the gradient. *Am Psychol.* 1994; 49(1): 15-24. doi: 10.1037/0003-066X.49.1.15

13. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. *Health Aff (Millwood).* 2002; 21(2): 60-76. doi: 10.1377/hlthaff.21.2.60

14. Cutler DM, Lleras-Muney A, Vogl T. Socioeconomic status and health: dimensions and mechanisms. http://www.nber.org/papers/w14333. National Bureau of Economic Research working paper 14333. Published September 2008. Accessed February 10, 2016.

15. Williams DR, Collings C. US socioeconomic and racial differences in health: patterns and explanations. *Annu Rev Sociol.* 1995; 21: 349-386. https://sph.umich.edu/sep/downloads/Williams_and_Collins.pdf. Accessed February 10, 2016.

16. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *Br Med Bull.* 2007; 81-82: 21-37. doi: 10.1093/bmb/ldm001

17. Lantz PM, Lynch JW, House JS, et al. Socioeconomic disparities in health change in longitudinal study of US adults: the role of health-risk behaviours. *Soc Sci Med.* 2001; 29-40. doi: 10.1016/S0277-9536(00)00319-1

18. Rani M, Bonu S, Jha P, Nguyen SN, Jamjoum L. Tobacco use in India: prevalence and predictors of smoking and chewing in a national cross sectional household survey. *Tob Control.* 2003; 12:e4. doi: 10.1136/tc.12.4.e4

19. Subramanian SV, Smith GD, Subramanyam M. Indigenous health and socioeconomic status in India. *PLoS Med.* 2006; 3(10): 1794-1804. doi: 10.1371/journal.pmed.0030421

20. Gajalaksmi V, Whitlock G, Peto R. Social inequalities, tobacco chewing, and cancer mortality in south India: a case-control analysis of 2,580 cancer deaths among non-smoking non-drinkers. *Cancer Causes Control.* 2012; 23 Suppl 1: 91-98. doi: 10.1007/s10552-012-9905-1

21. Rahu K, Parna K, Palo E, Rahu M. Contrasts in alcohol-related mortality in Estonia: education and ethnicity. *Alcohol Alcohol.* 2009; 44(5): 517-522. doi: 10.1093/alcalc/agp035

22. Pridemore WA, Tomkins S, Eckhardt K, Kiryanov N, Saburova L. A case-control analysis of socio-economic and marital status differentials in alcohol and non-alcohol related mortality among working-age Russian males. *Eur J Public Health.* 2010; 20(5): 569-575. doi: 10.1093/eurpub/ckq019

23. Tjepkema M, Wilkins R, Long A. Cause-specific mortality by education in Canada: a 16-year follow-up study. *Health Rep.* 2012; 23(3): 23-31.

24. Jha P, Jacob B, Gajalakshmi V, et al. A Nationally Representative Case–Control Study of Smoking and Death in India. *N Engl J Med.* 2008; 358: 1137-1147. doi: 10.1056/NEJMsa0707719

25. Vineis P, Alavanja M, Buffler P, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst.* 2004; 96(2): 99-106. doi: 10.1093/jnci/djh014

26. Ramadas K, Sauvaget C, Thomas G, Fayette JM, Thara S, Sankaranarayanan R. Effect of tobacco chewing, tobacco smoking and alcohol on all-cause and cancer mortality: A cohort study from Trivandrum, India. *Cancer Epidemiol.* 2010; 34(4): 405-426. doi: 10.1016/j.canep.2010.04.006

27. Gu D, Kelly TN, Wu X, et al. Mortality Attributable to Smoking in China. *N Engl J Med.* 2009; 360: 150-159. doi: 10.1056/NEJMsa0802902

28. Gajalakshmi V, Peto R, KanakaTS, Jha P. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43 000 adult male deaths and 35000 controls. *Lancet.* 2003;362(9383):507-515.doi:10.1016/S0140-6736(03)14109-8

29. Thun MJ, Apicella LF, Henley SJ. Smoking vs other risk factors as the cause of smoking-attributable deaths: confounding in the courtroom. *JAMA.* 2000; 284(6): 706-712. doi: 10.1001/jama.284.6.706

30. Henley SJ, Thun MJ, Connell C, Calle EE. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control.* 2005; 16: 347-358. doi: 10.1007/s10552-004-5519-6

31. Ministry of Health and Family Welfare Government of India. International Institute for Population Sciences, Deonar, Mumbai. National Family Health Survey (NFHS-3), 2005–06: Volume 1. https://dhsprogram.com/pubs/pdf/FRIND3/FRIND3-Vol1AndVol2.pdf. Published September 2007. Accessed February 10, 2016.

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-103

Brief Research Report

*Corresponding author
Guilherme Caetano Garcia
Veterinarian
Post Graduation Program in Animal Production and Sanity in the Tropics
Universidade de Uberaba
Av. Nenê Sabino, 1801
Bairro Universitário, Brazil
E-mail: guilhermecgarcia@yahoo.com.br

Volume 1 : Issue 1
Article Ref. #: 1000EPOJ1103

Article History
Received: September 14th, 2015
Accepted: March 7th, 2016
Published: March 9th, 2016

Citation
Garcia GC, de Moura DM, Frange RCC, Bitta ER, Bittar JFF. Bovine trypanosomiasis: retrospective investigation and clinical signs. *Epidemiol Open J*. 2016; 1(1): 16-19. doi: 10.17140/EPOJ-1-103

Bovine Trypanosomiasis: Retrospective Investigation and Clinical Signs

Guilherme C. Garcia[1*]; Dênia M. de Moura[2]; Renata C. C. Frange[1]; Eustáquio R. Bittar[2]; Joely F. F. Bittar[2]

[1]Post Graduation Program in Animal Production and Sanity in the Tropics, UNIUBE/FAZU/ABCZ. Av. Nenê Sabino, 1801 38055-500, Uberaba-MG, Brazil
[2]Professor of the Veterinary Medicine Course UNIUBE/FAZU/ABCZ. Av. Nenê Sabino, 1801 38055-500, Uberaba-MG, Brazil

ABSTRACT

Trypanosoma vivax is a protozoan that causes Bovine tripanosomiasys. Originally from Africa, the disease has become common in other countries. Bovine trypanosomiasis is a disease underdiagnosed in many parts of the world, including Brazil. The lack of knowledge regarding this protozoan is a factor that contributes to the rapid spread of the disease. Many losses are attributed to the disease, including death of animals. This study aimed to perform a retrospective investigation of cattle with *T. vivax* that had blood samples forwarded to Veterinary Hospital of Uberaba-Brazil by performing the *Buffy coat* technique. The collected data showed that in 285 suspected animals, that had samples submitted to Hospital Veterinário de Uberaba, 17.54% were positive. Separating in gender, females had 22.37% of positivity rate and males 2.13%, which is explained by the handling of the animals where handlers are able to see signs of the disease and decreased milk production, besides the use of the same needle for oxytocin application before milking that spreads the disease for many animals in a short period of time. The biggest prevalence among ages was seen in animals between 1 to 12 months (35% of positivity) and 12 to 24 months of age (61.64% of positivity), possibly because of the immune system development, younger animals do not have immunity to the disease. The breed that most showed positivity was Holstein dairy breed (100%). The opportune diagnosis of *T. vivax* is an important finding since the disease leads to large losses in cattle ranching and prejudices the economic system.

KEYWORDS: *Trypanosoma vivax*; Bovine trypanosomiasis; Diagnostic; *Buffy coat.*

INTRODUCTION

Bovine trypanosomiasis is a parasitic disease caused by *Trypanosoma (Dutonella) vivax* that mainly affects ungulates, including cattle, sheep, goats, horses, camels and various species of wild antelope and buffalo.[1,2]

In West Africa, *T. vivax* is an important and pathogenic trypanosome in cattle, being a significant disease to animal breeding transmitted by the tsetse fly (*Glossina* spp). In Latin America, mechanical vectors transmit the parasite.[3,4] In Brazil, *T. vivax* was first identified in a buffalo in Pará state, subsequently to an outbreak of trypanosomiasis in Pantanal affecting 10 of 29 head of cattle.

Symptoms depend on the degree of the disease.[5] Often is observed hyper acute infection, characterized by severe anemia, bleeding in mucous surface and thrombocytopenia arising.[6] Acute infection, which generates septicemia with fever and marked parasitemia two weeks after infection, may result in death.[7] It is possible to find ecchymotic hemorrhages,[5] intermittent fever, swollen lymph nodes, tachycardia, poor body condition, decreased fertility,[8,9] leukopenia, watery eyes, progressive weakness, abortions[9] and anemia without hemoglobinuria.[5]

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-103

Observing fresh blood under microscope is a direct method adequate to diagnose the acute disease.[5] In contrast, the chronic phase of the disease is diagnosed by detection of antibodies against *T. vivax* using the indirect immunofluorescence.[10,11]

This study aimed to perform a retrospective investigation of cattle with *T. vivax* n Veterinary Hospital of Uberaba-Brazil.

MATERIAL AND METHODS

A retrospective study was performed with 285 bovine from Uberaba (152 animals), Prata (90 animals), Pirajuba (20 animals), Campo Florido (7 animals), Veríssimo (6 animals), Comendador Gomes (4 animals), Monte Alegre de Minas (3 animals), Frutal (2 animals) and Coromandel (1 animal) that had samples forwarded to Hospital Veterinário de Uberaba from May, 2012 to September, 2013. The animals were separated according to gender being 47 males, 219 females and 19 did not have specified gender. The bovines also had different breeds, being Holstein (4 animals), Gyr (8 animals), Girolando (180 animals) and undefined cattle breed (93 animals). In addition, the animals were also separated according to ages.

The protozoan was detected by *Buffy coat* technique that consists in centrifuging the blood to be analyzed in a closed hematocrit micro tube. After centrifugation, the tube is broken between cellular and liquid part and a small portion of material is deposited on the slide, according to the technique described.[11] The slides were stained with Quick Panoptic® kit and visualized in an optical microscope at 100X objective with immersion oil. The animals were considered positive when was possible to observe trypomastigote form (Figure 1). The data were analyzed by descriptive statistics.

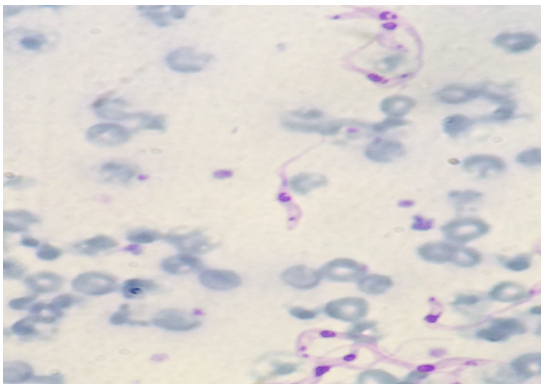


Figure 1: Positive animal for *Trypanosoma vivax* using smear made by *Buffy coat* technique (trypomastigote form). 100X magnification stained with quick Panoptic®.

RESULTS AND DISCUSSION

The Triângulo Mineiro region is located in state of Minas Gerais – Brazil. This region is one of the most important sites for the production of cattle and exports genetic material to different places around world and there is little study about this parasitosis in Minas Gerais state.

The *T. vivax* occurrence in different months of the year is shown in figure 2. The protozoan epidemiology is directly related to the rainfall period.[4,11,12] Recent studies[13] analyzed the positivity percentage of animals from Uberaba found 16.2% of positivity when searching for antibodies anti-*T. vivax*, value that was near to what was found in the present study.

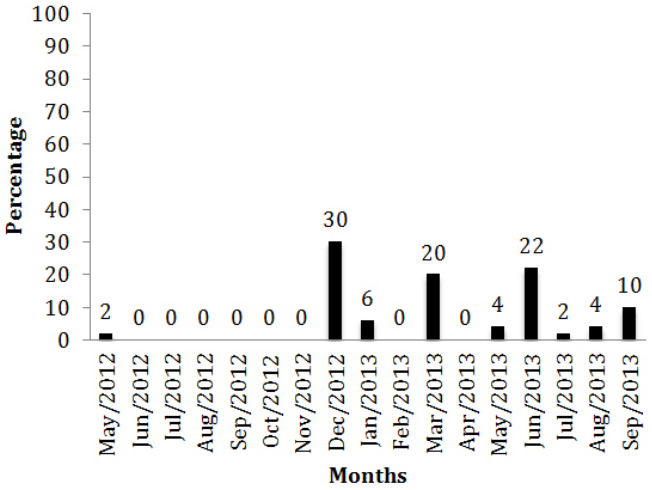


Figure 2: Percentage of positive and negative animals to *T. vivax* in different months.

Males showed 2% (1) positivity, lowered when compared to females 98% (49) (Figure 3A). The highest *T. vivax* occurrence in females is explained firstly because of the stress to which they are submitted,[14] i.e. Gestation, lactation, and secondly because females are more likely to contamination with fomites i.e. when the same needle is used for many animals in application of medication such as oxytocin before milking.

When the *T. vivax* occurrence in the region of Uberaba and adjacent regions was studied,[13] was shown that in 91.6% of positive properties for *T. vivax* the needle exchange between animals while administrating drugs was not done.

In the present study Girolando animals had 72% (36) positivity followed by not specified breeds 16% (8), Holstein breed, which had 8% positivity (4). Gyr breed had 4% (2) positivity (Figure 3B). The first trypanosomiasis report in dairy herd for the southwest region was described in recent studies[15] in the state of São Paulo, reporting animals breed Holstein and Girolando. In the state of Minas Gerais the first report was done in 2008.[16] Other breeds were described with infection such as Brahman.[17] Some breed developed what is called trypanotolerancy, which is the resistance to the infection and keep in the condition of asymptomatic carrier.[18]

The fact that the animals from the present study are in the most part dairy cattle is because the region of Minas Gerais is a pole in milk production, having big dairy herds and being the

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-103

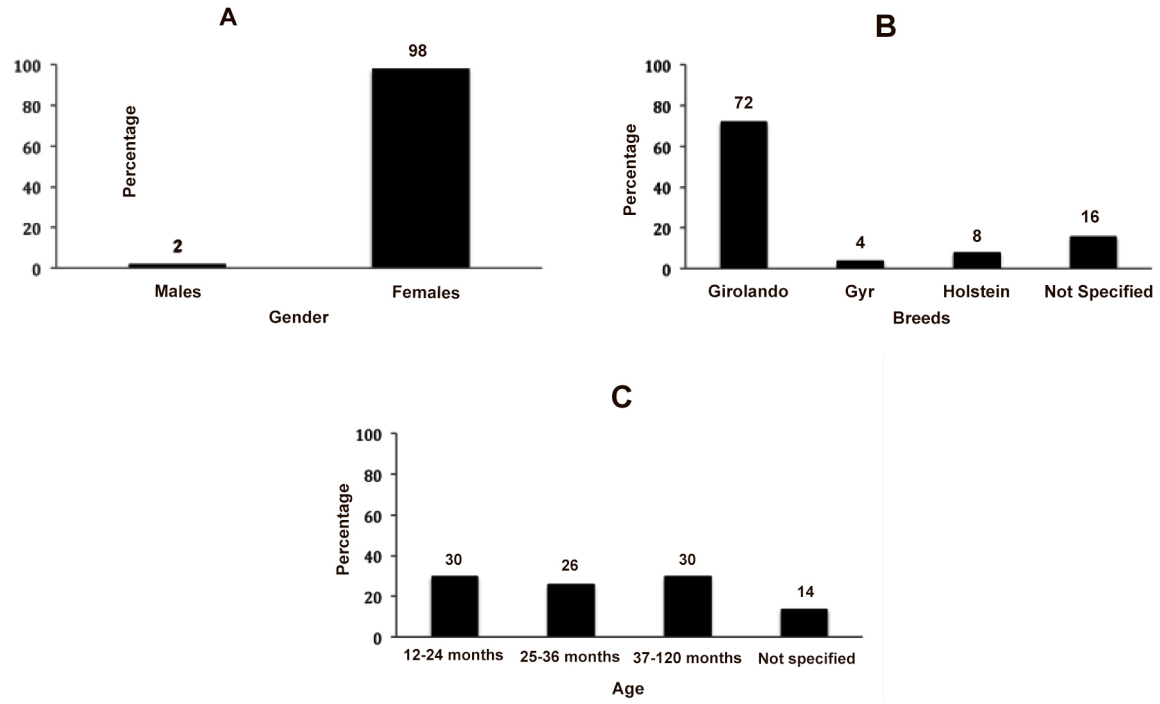


Figure 3: A - Percentage of positive and negative animals to *T. vivax* in males and females; B - Occurrence of positive animals for *T. vivax* among the different breeds; C - Percentage of positive animals among different ages.

main state in milk production in Brazil.[19]

The diagnosis in dairy cattle is easier, once the milk production is hampered,[4] being promptly noticed for those who are handling the animals daily.

The animals were separated in groups according the age, being 30% (15) older than 12 months, 26% (13) between 25 to 36 months, 30% (15) between 37 to 120 months and14% (7) did not have the age identified (Figure 3 C).

The resistance to the protozoan besides other factors can vary with age.[14] This could be explained because younger animals do not have developed immunity to the pathology, being the first contact within the first months of life, what lead to acute cases that were detectable to the *buffy coat* method.

It is important to emphasize that the *Buffy coat* technique allows detecting circulating parasite, i.e., in the acute phase or when the animal undergoes immunosuppression. Much of infections in cattle from endemic areas tend to be chronic course and not always fatal.[20]

In South America, *T. vivax* transmission is mechanical. This work shows that even without the presence of the tsetse fly, there are bovine trypanosomiasis cases in Brazil, with severe symptoms attributed mainly to *Tabanidae*. In addition, the mechanical transmission by fomites is relatively easy. Brazil is an important pole in the production chain of animals. For this reason attention should be taken aiming the control of this agent in farms of the country.[21]

CONFLICTS OF INTEREST: None.

REFERENCES

1. Batista JS, Rodrigues CMF, Olinda RG, et al. Highly debilitating natural Trypanosoma vivax infection in Brazilian calves: epidemiology, pathology, and probable transplacental transmission. *Parasitol Res*. 2012; 110(1): 73-80. doi: 10.1007/s00436-011-2452-y

2. Bowman DD. *Georgi's Parasitology for Veterinarians*. 9th ed. St. Louis, Missouri, USA: Saunders Elsevier; 2009: 451.

3. Adam Y, Marcotty T, Cecchi G, et al. Bovine trypanosomosis in the upper west region of ghana: entomological, parasitological and serological cross-sectional surveys. *Res Vet Sci*. 2012; 92(3): 462-468. doi: 10.1016/j.rvsc.2011.04.004

4. Batista JS, Bezerra FSB, Lira RA, et al. Aspectos clínicos, epidemiológicos e patológicos da infecção natural em bovinos por Trypanosoma vivax na Paraíba [In portugese]. *Pesquisa Veterinária Brasileira*. 2008; 28(1): 63-69. doi: 10.1590/S0100-736X2008000100010

5. Coetzer JAW, Thomson GR, Tustin RC. *Infectious diseases of Livestock*. Vol. 1. Cape Town, South Africa: Oxford University Press; 1994: 729.

6. Fieldman BF, Zinkl JG, Jain NC. *Schalm's Veterinary Hematology*. 5th ed. Baltimore, Maryland, USA: Lippincott Williams

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-103

& Wilkins; 2000: 1344.

7. Jain CN. *Essentials of veterinary hematology*. PA, USA: Lea & Febiger; 1993: 417.

8. OzórioA LAR, Madruga CR, Desquesnes M, Soares CO, Ribeiro LRR, da Costa SCG. Trypanosoma (Duttonella) vivax: its biology, epidemiology, pathogenesis, and introduction in the New World – a review. *Mem Inst Oswaldo Cruz*. 2008; 103(1): 1-13. doi: 10.1590/S0074-02762008000100001

9. da Silva AS, Costa MM, Polenz MF, et al. First report of Trypanosoma vixax in bovines in the State of Rio Grande do Sul, Brazil [In portugese]. *Cienc Rural*. 2009; 39(8): 2550-2554. doi: 10.1590/S0103-84782009005000189

10. Abraão DC, de Carvalho AU, Filho EJF, Bartholomeu DC, Ribeiro MFB. Aspectos clínicos e patológicos da infecção natural em bovinos leiteiros por Trypanosoma vivax em Minas Gerais, Brasil [In portugese]. *Ciência Animal Brasileira*. 2009; 1: 666-671.

11. Silva RAMS, Andrew S, Ramirez L, DÁVILA AMR. *Trypanosoma evansi e Trypanosoma vivax: biologia, diagnóstico e controle* [In portugese]. Circular Técnico. MS, Brazil: Embrapa Pantanal. 2002: 141.

12. Barros T, Foil L. Seasonal occurrence and relative abundance of Tabanidae (Diptera) from the Pantanal region, Brazil. *Memoirs on Entomology International*. 1999; 14: 387-396.

13. Franger RCC, Bittar ER, Bittar JFF, Campos MTG. *Tripanossomíase em vacas da microrregião de Uberaba – MG: estudo soroepidemológico* [dissertation] [In portugese]. Uberaba - MG, Brazil: Mestrado em Produção e Sanidade Animal, Universidade de Uberaba; 2013.

14. Schenk MAM, Mendonça CL, Madruga CR, Kohayagawa A, Araújo FR. Avaliação clínico laboratorial de bovinos Nelore infectados experimentalmente com Trypanosoma vivax [In portugese]. *Pesq Vet Bras*. 2001; 21(4): 157-161. doi: 10.1590/S0100-736X2001000400006

15. Cadioli FA, Barnabé PA, Machado RZ, et al. First report of Trypanosoma vivax outbreak in dairy cattle in São Paulo state, Brazil. *Rev. Bras. Parasitol. Vet*. 2012; 21(2): 118-124. doi: 10.1590/S1984-29612012000200009

16. Carvalho AU, Abraão DC, Facury Filho EJ, Paes PRO, Ribeiro MFB. Occurrence of Trypanosoma vivax in Minas Gerais state, Brazil. *Arq. Bras. Med. Vet. Zootec*. 2008; 60(3): 769-771. doi: 10.1590/S0102-09352008000300037

17. Linhares GFC, Dias de Carvalho Dias F, Fernandes PR, Duarte SC. Tripanossomíase em bovinos no município de Formoso do Araguaia. Tocantins (relato de caso) [In portugese]. *Ciência Animal Brasileira*. 2006; 7(4): 455-460.

18. Mattioli RC, Wilson RT. Trypanosomes, tsé-tsé and trypanotolerance: coevolution in Tropical Africa. *Parassitologia*. 1996; 38(3): 531-535.

19. Cuglovici DA, Bartholomeu DC, Reis-Cunha JL, Carvalho AU, Ribeiro MF. Epidemiologic aspects of an outbreak of Trypanosoma vivax in a dairy cattle herd in Minas Gerais state, Brazil. *Vet Parasitol*. 2010; 169(3-4): 320-326. doi: 10.1016/j.vetpar.2009.12.041

20. Radostidis OM, Gay CC, Blood DC, Hinchcliff KW. Clínica veterinária: um tratado de doenças dos bovinos, ovinos, suínos, caprinos e equinos [In portugese]. 9th ed. Rio de Janeiro, Brazil: Guanabara Koogan; 2002: 1737.

21. Riet-Correa F, Schild AL, Lemos RAA, Borges JR. *Doenças dos ruminantes e equídeos* [In portugese]. Santa Maria, Brazil: Pallotti; 2001: 999.

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

Research

*Corresponding author
Michelle A. Morris, PhD
Leeds Institute for Data Analytics
University of Leeds
Level 11, Worsley Building
Leeds, LS2 9JT, UK
Tel. +44 (0) 113 343 0883
E-mail: m.morris@leeds.ac.uk

Volume 1 : Issue 1
Article Ref. #: 1000EPOJ1104

Article History
Received: January 6th, 2016
Accepted: March 19th, 2016
Published: March 21st, 2016

Citation
Morris MA, Clarke GP, Edwards KL, Hulme C, Cade JE. Geography of diet in the uk women's cohort study: A cross-sectional analysis. *Epidemiol Open J*. 2016; 1(1): 20-32. doi: 10.17140/EPOJ-1-104

Geography of Diet in the UK Women's Cohort Study: A Cross-Sectional Analysis

Michelle A. Morris, PhD[1*]; Graham P. Clarke, PhD[2]; Kimberley L. Edwards, PhD[3]; Claire Hulme, PhD[4]; Janet E. Cade, PhD[5]

[1]Leeds Institute for Data Analytics, University of Leeds, Leeds, LS2 9JT, UK
[2]School of Geography, University of Leeds, Leeds, LS2 9JT, UK
[3]Centre for Sports Medicine, School of Medicine, University of Nottingham, Queens Medical Centre, Nottingham, NG7 2UH, UK
[4]Academic Unit for Health Economics, Leeds Institute of Health Sciences, University of Leeds, LS2 9JT, UK
[5]Nutritional Epidemiology Group, School of Food Science and Nutrition, University of Leeds, Leeds, LS2 9JT, UK

ABSTRACT

Diet can influence health outcomes and chronic disease risk, therefore a better understanding of factors influencing diet is important in promotion of healthier dietary choices. Many factors influence food choice, including the environment in which we live. This study aims to explore differences in dietary pattern consumption by two spatial measures: Government Office Region (a large regional unit of geography) and Output Area Classification (a small area geography combined with demographic characteristics). A cross-sectional analysis using data from the UK Women's Cohort Study was carried out. This cohort included ~35000 middle aged women recruited between 1995 and 1999. Dietary patterns were derived using a k-means cluster analysis from diet data collected using a validated 217 item Food Frequency Questionnaire. Multinomial logit regression was used to test whether the area in which the women live, predicts their dietary pattern consumption. Results show that dietary patterns vary significantly by both spatial measures. The Government Office Region, the North West of England has the highest proportion of individuals consuming the least healthy, monotonous diets, while Greater London has the highest proportion of vegetarian diets. Individuals living in Supergroups 'Countryside' and 'Prospering Suburbs' consume healthier, more diverse diets. Those in 'Constrained by Circumstance' and 'Blue Collar Communities' consume monotonous, less healthy diets. Using a combination of spatial scales such as Government Office Region and Output Area Classification Supergroup could have a beneficial impact on targeting of public health dietary interventions and subsequent health.

KEYWORDS: Dietary pattern; Diet; Geodemographic classification; Geography; Region; UK women's cohort study; Public health.

ABBREVIATIONS: NDNS: National Diet and Nutrition Survey; GOR: Government Office Region; OAC: Output Area Classification; UKWCS: UK Women's Cohort Study; FFQ: Food Frequency Questionnaire; NHS: National Health Service; METs: Metabolic Equivalent of Tasks; RRRs: Relative Risk Ratios; CI: Confidence Interval; WCRF: World Cancer Research Fund; GP: General practitioner.

BACKGROUND

Dietary consumption can have an impact on long-term health around the world.[1-3] Diet is a modifiable risk factor in a number of chronic diseases: for example, type II diabetes, coronary heart disease, cardiovascular disease, hypertension and obesity.[3]

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

Diet is a complex phenomenon. A single food is not eaten in isolation, but in combination with others. Interaction between foods can affect how they are absorbed and processed by the body which may subsequently affect health. Analysis of common dietary patterns is therefore particularly relevant to explore links between diet and health. The contents of a dietary pattern can vary widely from the differentiation between two main types of diet; omnivores and vegetarians[4] to patterns such as a Mediterranean diet[5,6] and data driven patterns specific to a particular population, assigned by a cluster analysis.[7]

Influences on dietary patterns span a broad spectrum entwining social, economic, demographic, environmental and individual factors.[8-12] Using geographical units is one way which some of these can be incorporated into health research. An ecological model framework to investigate how individuals and their environments interact is well documented.[13-15] However, unpicking such complex relationships is challenging. The use of a geodemographic classification goes some way towards accounting for social (compositional) and environmental (context) interactions by grouping people with similar demographic and neighbourhood characteristics residing in small geographical units together. Applying a geodemographic classification to existing cohort data unlocks the potential for addressing new and important research questions. The geographical location (in this study GOR) can only account for environment context as there are no demographic characteristics included.

The UK Women's Cohort Study (UKWCS) is a large cohort established to investigate associations between diet and health in the UK.[16] Data is available at the post code level (a small spatial unit) which can be aggregated to a number of larger geographical units. The cohort targeted only women as at the time of cohort inception women were not well represented in large UK cohort studies. With rich diet and health outcome data in the UKWCS it is possible to describe dietary patterns at various spatial scales and provide important information about the type of people, living in types of neighbourhoods, consuming different dietary patterns which could be linked to spatial variations in future health outcomes; and because a standard classification is used would be generalisable to women in the UK population.

The aim of this paper is to explore variations in dietary patterns in women across the UK in two ways: at the large scale GOR level and using a geodemographic classification for a smaller scale picture. Results at the two spatial scales will be compared and contrasted with regards to their application and usefulness in a health setting. If a better understanding of dietary habits in specific groups of people can be developed then there is the potential to provide dietary interventions which could benefit many in terms of health and wellbeing in addition to prevention of chronic diseases.

METHODS

Study Design and Sample

At baseline, between 1995 and 1998, 35,372 women were recruited into the UKWCS on a volunteer basis from a World Cancer Research Fund (WCRF) mailing list. The response rate was 58%, from 61,000 invitations to take part. These women all completed at baseline first contact, a 217 item validated,[17] Food Frequency Questionnaire (FFQ), aiming to assess usual diet over the past 12 months, along with a more general questionnaire. It was not possible to assign a dietary pattern to all women due to some providing incomplete FFQs and therefore 1902 women were excluded from the sample. Individuals consuming <500 and >6000 kcal/day were excluded from the analysis as these were considered to be outliers (n=70). A valid postcode was not available for all these women, so following data cleaning these 1128 women were excluded. Finally, 62 women living in Northern Ireland were also excluded due to insufficient numbers in this area for meaningful analysis. This left a sample of 32,205 for cross-sectional dietary pattern analysis.

Ethics

Ethical approval was obtained from 174 National Health Service (NHS) local research ethics committees during 1994 and 1995.[18]

Dietary patterns

The dietary patterns in the UKWCS were identified in a previous study by Greenwood et al.[7] Seven dietary patterns were identified from FFQ data using a k-means cluster analysis. The patterns were named to reflect the types and quantities of food consumed in each pattern. The patterns are as follows: "Monotonous Low Quantity Omnivore" – a diet high in white bread, sugar and milk; "Health Conscious" – a diet high in fruit and vegetables and wholegrains; "Traditional Meat Chips and Pudding Eater" – typified by a white bread, meat, chips and high fat, creamy foods; "Conservative Omnivore" – a diet lacking high quantities of any food, but with moderate quantities of most foods, especially potatoes, meat, fish, eggs, fruit and vegetables; "Higher Diversity Traditional Omnivore" – a diet similar to the Traditional Meat Chips and Pudding eater but with higher diversity; "Low Diversity Vegetarian" – a meat free diet high in wholemeal bread, soya, pulses, fruit and vegetables; and "High Diversity Vegetarian" – a meat free diet with lots of variety including wholemeal bread, cereals, wholemeal pasta and rice, soya, spreads, nuts, pulses, fruit, vegetables and more (see Appendix A - Summary of dietary patterns for more details of the dietary patterns). The "Health Conscious" dietary pattern is the healthiest pattern and the "Monotonous Low Quantity Omnivore" the least healthy. The healthiness of the dietary patterns was determined by scoring each pattern against the UK dietary recommendations 'The Eatwell Plate'.[19]

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

Spatial scale

This study first reports diet according to the nine GORs of England. Scotland and Wales are included as entire countries (without further regional breakdown). Northern Ireland has not been included (as described above). Therefore 11 regions are presented. The OAC[20] is used for the geodemographic analysis. This classification has been created using the geographical unit Output Area – which consists of a minimum of 40 households and contains an average of 250 people – combined with 41 variables reported in the 2001 census. This was the census closest in time to the majority of the UKWCS data collection. OAC is a three tier classification. The first tier are named 'Supergroups' of which there are seven. The second tier 'Groups' of which there are 21 and the third tier 'Subgroups' of which there are 52. The OAC categories were generated using an adapted k-means clustering procedure.[20] Results at Supergroup level are presented in this paper. The seven OAC Supergroups are as follows: 'Blue Collar Communities' – typified by living in terraced accommodation, presence of young children and routine or semi-routine employments along with those working in manual labour type roles; 'City Living' – typically including high proportions of adults aged 25-44, large numbers of individuals born outside of the UK, single person rented houses or flats and many in or holding higher education qualifications; 'Countryside' – this groups contains high proportions of adults aged over 45 years old, living in detached housing with two or more cars in the household. Many work from home, provide unpaid care or work in agriculture; 'Prospering Suburbs' – many aged 45-64 living as two adults and no children reside in these areas. There are non-dependent children living in these areas in mostly detached housing with two or more cars per household; 'Constrained by circumstance' – this Supergroup is typified by individuals living in care homes, or public provided accommodation, as such there are many divorced or separated, single pensioners, or lone parent households and those who are unemployed or with limiting long-term illness; 'Typical Traits' – this groups contains those with most average characteristics; and 'Multicultural' – this group has high proportions of those born outside the UK with a range of different ethnicities. Many will use public transport or be unemployed (see Appendix B – Summary of OAC Supergroups for more information).

GOR and OAC were assigned *via* the postcode unit for each woman in the cohort, using the geoconvert tool.[21]

Covariates

Metabolic Equivalent of Tasks (METs) were used as a measure of physical activity, calculated by assigning a value from the Compendium of Physical Activities[22] to the results of questions asked at baseline where the women reported hours per typical week spent in various common activities. Smoking is reported as a binary value which indicates if the woman was a current smoker at baseline. Total calorie intake, including calories from alcohol, is derived from the FFQ. Age, social class and education were collected in the UKWCS baseline lifestyle questionnaire.

Statistical analysis

STATA IC 12.1 statistical software has been used for the analysis.[23] Chi squared statistics are used to detect differences across categories for tabulated data.

Multinomial logit regression was carried out for the categorical data. The regression analysis looked at the likelihood of consuming a particular dietary pattern compared to the "Traditional Meat Chips and Pudding Eater" pattern (the most commonly consumed in the UKWCS) accounting for place of residence. In the regional analysis the region of residence was compared to living in the South East, (where the majority of the UKWCS women reside). The geodemographic analysis compared the Supergroup which the women live in with women living in the Typical Traits Supergroup (named since those residing in such areas are average with respect to the demographic variables used to create the classification). Results are presented as Relative Risk Ratios (RRRs) with 95% confidence intervals and *p* values.

Regression models are adjusted to account for potential confounders which were identified using a causal diagram. The adjusted regression model includes physical activity, smoking and total calorie intake including alcohol, age, social class and education. The composition characteristics – age, social class and education – were not adjusted for in the analysis with OAC (Table 2) as this would have over adjusted these characteristics as they are included in the OAC already.

RESULTS

Summary statistics

The UKWCS mean age was 52.2 years (SD 9.3) with means ranging between 51.4 to 53.0 years by region and 50.1 to 53.4 years by OAC Supergroup. Physical activity, measured using METS calculated from a physical activity questions for a 24 hour period had a mean value of 16.0 METS (SD 11.7); mean regional range 16.4 to 17.8; OAC Supergroup range 15.0 to 18.2. Sixty-five percent of the cohort had a professional/managerial occupation with a regional range of 58-67% and OAC Supergroup range of 53-73%, with highest numbers in the City Living Supergroup and lowest in the Blue Collar Communities. Fifty-two percent of the cohort were educated to A-level (school year 13) or above with a regional range of 46-65% and OAC Supergroup range 37-70% with lowest values in the 'Constrained by Circumstance' and 'Blue Collar Communities' and highest again in 'City Living'.

A wider variation in the mean characteristics of the women is evident when grouped by OAC Supergroup compared to grouping by region. This supports the expectation that incor-

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

porating demographic variables into a geographical classification enhances understanding of specific populations, rather than seeing averaged out characteristics of a much larger geographical region.

Regional analysis

The distribution of the UKWCS as a percentage of the total UK population of women, by region, ranges from 0.08% for the North East, North West and Scotland and 0.17% for the South East and South West (with other regions falling in-between). So whilst the lowest number of cohort women reside in the North East, this is also the region which has the lowest population in the whole UK. The dietary pattern consumption vary significantly across regions (p=0.002), with the exception of the Health Conscious dietary pattern (Figure 1), however, differences are small.

Results from a multinomial regression analysis (Table 1), for dietary pattern consumption by region, identify that some regions are more likely to consume certain dietary patterns over others. However, the regression results show that no region has overall better dietary habits than another. Greater London highlights how one region can exhibit statistical significance in relative risk ratio (RRR) of being more likely to consume "Health Conscious" (most healthy) and also more likely to consume a "Monotonous Low Quantity Omnivore" (least healthy)[19] diet compared to the "Traditional Meat, Chips and Pudding Eater" pattern, which was the reference group, showing that both extremes of dietary patterns reside in the same region. While some regions show a significant increased likelihood of consuming a poor "Monotonous Low Quantity Omnivore" dietary pattern; for example, Wales, Yorkshire and the Humber, North West; these regions are, however, not significantly less likely to consume a "Health Conscious" dietary pattern which would make it difficult to know where to precisely target healthy dietary pattern promoting interventions.

These observations remain true when the model is adjusted for physical activity and energy intake and smoking and for demographic characteristics; age, social class and education and show much the same results, in some cases slightly accen-

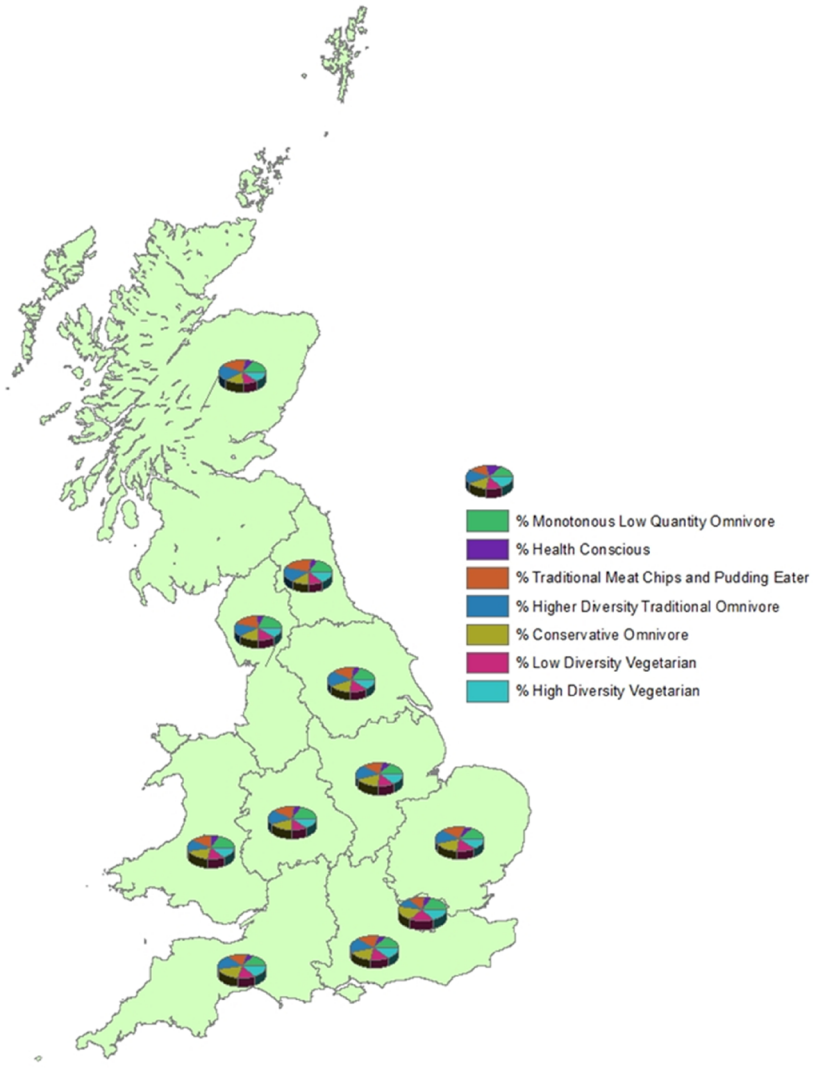


Figure 1: Percentage of UKWCS consuming each dietary pattern by GOR.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

	Monotonous Low Quantity Omnivore	Health Conscious	Traditional Meat Chips and Pudding Eater	Higher Diversity Traditional Omnivore	Conservative Omnivore	Low Diversity Vegetarian	High Diversity Vegetarian
	RRR (95% CI) *p* value	**RRR (95% CI) *p* value**	**Ref.**	**RRR (95% CI) *p* value**	**RRR (95% CI) *p* value**	**RRR (95% CI) *p* value**	**RRR (95% CI) *p* value**
Unadjusted model (pseudo R^2=0.003)							
North East	0.87(0.70 to 1.08) *p*=0.211	0.82(0.61 to 1.12) *p*=0.218	1.00	0.79(0.63 to 0.99) *p*=0.043	0.62(0.49 to 0.77) *p*<0.001	0.64(0.51 to 0.81) *p*<0.001	0.84(0.67 to 1.06) *p*=0.149
North West	1.20(1.04 to 1.38) *p*=0.013	0.91(0.75 to 1.12) *p*=0.368	1.00	0.81(0.69 to 0.94) *p*=0.006	0.85(0.73 to 0.98) *p*=0.023	0.84(0.73 to 0.98) *p*=0.025	0.83(0.71 to 0.98) *p*=0.024
Yorkshire and the Humber	1.11(0.95 to 1.30) *p*=0.179	0.97(0.78 to 1.20) *p*=0.776	1.00	1.07(0.92 to 1.25) *p*=0.392	0.96(0.83 to 1.12) *p*=0.646	0.90(0.77 1.06) *p*=0.199	0.99(0.84 to 1.17) *p*=0.873
East Midlands	1.01(0.85 to 1.18) *p*=0.944	1.15(0.93 to 1.42) *p*=0.209	1.00	1.07(0.91 to 1.25) *p*=0.444	1.13(0.97 to 1.32) *p*=0.123	0.92(0.78 to 1.09) *p*=0.340	1.00(0.84 to 1.19) *p*=0.997
West Midlands	1.07(0.92 to 1.25) *p*=0.384	1.05(0.85 to 1.30) *p*=0.652	1.00	0.88(0.75 to 1.04) *p*=0.135	1.03(0.89 to 1.19) *p*=0.713	0.82(0.70 to 0.97) *p*=0.019	0.96(0.81 to 1.13) *p*=0.610
East of England	0.89(0.76 to 1.03) *p*=0.115	0.92(0.75 to 1.12) *p*=0.407	1.00	0.94(0.81 to 1.09) *p*=0.400	0.98(0.85 to 1.12) *p*=0.736	0.89(0.77 to 1.03) *p*=0.124	0.89(0.76 to 1.05) *p*=0.169
Greater London	1.42(1.23 to 1.64) *p*<0.001	1.38(1.14 to 1.67) *p*=0.001	1.00	0.89(0.76 to 1.05) *p*=0.165	1.28(1.12 to 1.48) *p*<0.001	1.77(1.54 to 2.04) *p*<0.001	1.64(1.41 to 1.90) *p*<0.001
South East	1.00	1.00	1.00	1.00	1.00	1.00	1.00
South West	1.01(0.89 to 1.16) *p*=0.837	1.15(0.96 to 1.38) *p*=0.120	1.00	1.11(0.97 to 1.27) *p*=0.142	1.04(0.92 to 1.19) *p*=0.528	0.99(0.86 to 1.13) *p*=0.847	1.20(1.04 to 1.38) *p*=0.011
Scotland	0.84(0.71 to 0.99) *p*=0.039	1.11(0.90 to 1.37) *p*=0.329	1.00	0.97(0.82 to 1.14) *p*=0.688	0.77(0.65 to 0.90) *p*=0.001	0.66(0.56 to 0.78) *p*<0.001	0.84(0.70 to 1.00) *p*=0.046
Wales	1.25(1.03 to 1.51) *p*=0.027	1.19(0.92 to 1.55) *p*=0.187	1.00	0.89(0.72 to 1.10) *p*=0.300	1.08(0.89 to 1.31) *p*=0.417	0.98(0.80 to 1.20) *p*=0.817	1.11(0.90 to 1.37) *p*=0.327
Adjusted model (adjusting for smoking, total calorie intake including alcohol, typical daily physical activity (METs), age, social class, education) (pseudo R^2= 0.12)							
North East	1.14(0.89 to 1.47) *p*=0.303	0.77(0.56 to 1.06) *p*=0.107	1.00	0.71(0.56 to 91) *p*=0.006	0.71(0.55 to 0.91) *p*=0.007	0.67(0.53 to 0.86) *p*=0.002	0.74(0.58 to 0.95) *p*=0.019
North West	1.48(1.25 to 1.74) *p*<0.001	0.91(0.73 to 1.12) *p*=0.368	1.00	0.76(0.64 to 0.90) *p*=0.001	0.95(0.81 to 1.11) *p*=0.525	0.90(0.77 to 1.06) *p*=0.206	0.81(0.68 to 0.96) *p*=0.016
Yorkshire and the Humber	1.27(1.06 to 1.53) *p*=0.009	0.95(0.75 to 1.20) *p*=0.676	1.00	1.03(0.87 to 1.23) *p*=0.712	1.05(0.89 to 1.25) *p*=0.571	0.92(0.77 to 1.09) *p*=0.323	0.96(0.80 to 1.15) *p*=0.636
East Midlands	1.09(0.90 to 1.32) *p*=0.363	1.10(0.87 to 1.38) *p*=0.429	1.00	1.07(0.90 to 1.28) *p*=0.433	1.19(1.00 to 1.41) *p*=0.046	0.95(0.80 to 1.14) *p*=0.590	0.96(0.80 to 1.15) *p*=0.658
West Midlands	1.16(0.97 to 1.38) *p*=0.105	1.02(0.81 to 1.27) *p*=0.879	1.00	0.86(0.72 to 1.03) *p*=0.094	1.01(0.85 to 1.19) *p*=0.949	0.79(0.66 to 0.94) *p*=0.008	0.91(0.76 to 1.09) *p*=0.316
East of England	0.90(0.76 to 1.07) *p*=0.229	0.96(0.77 to 1.20) *p*=0.721	1.00	1.00(0.85 to 1.17) *p*=0.987	0.98(0.84 to 1.14) *p*=0.764	0.84(0.07 to 0.99) *p*=0.038	0.91(0.77 to 1.08) *p*=0.270
Greater London	1.23(1.04 to 1.45) p=0.015	1.37(1.11 to 1.68) *p*=0.003	1.00	0.89(0.75 to 1.05) *p*=0.178	1.14(0.97 to 1.33) *p*=0.107	1.46(1.26 to 1.70) *p*<0.001	1.45(1.23 to 1.70) *p*<0.001
South East	1.00	1.00	1.00	1.00	1.00	1.00	1.00
South West	1.07(0.92 to 1.25) *p*=0.392	1.09(0.90 to 1.32) *p*=0.381	1.00	1.11(0.96 to 1.29) *p*=0.157	1.01(0.87 to 1.17) *p*=0.909	0.99(0.85 to 1.14) *p*=0.860	1.18(1.01 to 1.37) *p*=0.032
Scotland	1.06(0.88 to 1.28) *p*=0.550	0.89(0.71 to 1.11) *p*=0.305	1.00	0.80(0.67 to 0.96) *p*=0.014	0.83(0.70 to 0.99) *p*=0.044	0.63(0.53 to 0.76) *p*<0.001	0.68(0.56 to 0.81) *p*<0.001
Wales	1.49(1.31 to 1.69) *p*=0.002	1.06(0.80 to 1.41) *p*=0.670	1.00	0.77(0.61 to 0.97) *p*=0.026	1.15(0.93 to 1.43) *p*=0.194	1.00(0.81 to 1.25) *p*=0.988	0.97(0.78 to 1.22) *p*=0.823

Table 1: Regression models investigating whether Government Office Region predicts dietary patterns displaying Relative Risk Ratio (95% Confidence Interval) and *p* value.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

tuated. The pseudo R^2 value shows that the adjusted model explains 12% of variation in dietary pattern, compared to less than 1% in the unadjusted model. Most of this variation is explained by the energy intake adjustment.

Geodemographic analysis

The UKWCS comprises women from each of the seven OAC Supergroups, with some over-representation in the 'Prospering Suburbs' and 'Countryside' and under-representation in the 'Constrained by Circumstance', 'Blue Collar Communities' and 'Multicultural' Supergroups (Figure 2). This is as expected in a predominantly middle class cohort of women. That said, there are still large numbers in each of the Supergroups.

Significant variation for consumption of all dietary patterns by OAC Supergroup is observed (Figure 3). In general, variation is wider when considering differences by geodemographic Supergroup compared to by region, suggesting that the inclusion of demographic variables with geography could tell us something more interesting about dietary patterns.

The multinomial regression model (Table 2) shows that OAC Supergroup has a significant relationship with dietary pattern consumption. The unadjusted model shows that the 'Constrained by Circumstance' group have a significantly elevated

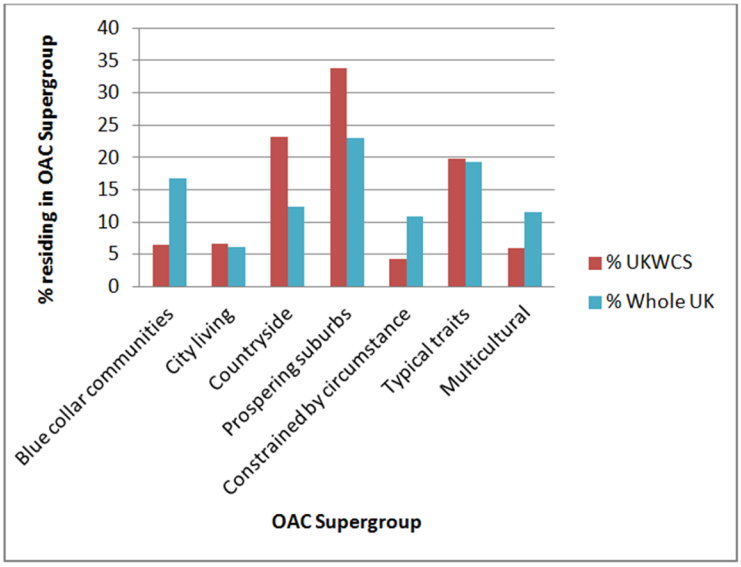


Figure 2: UKWCS compared to the UK population, by OAC Supergroup.

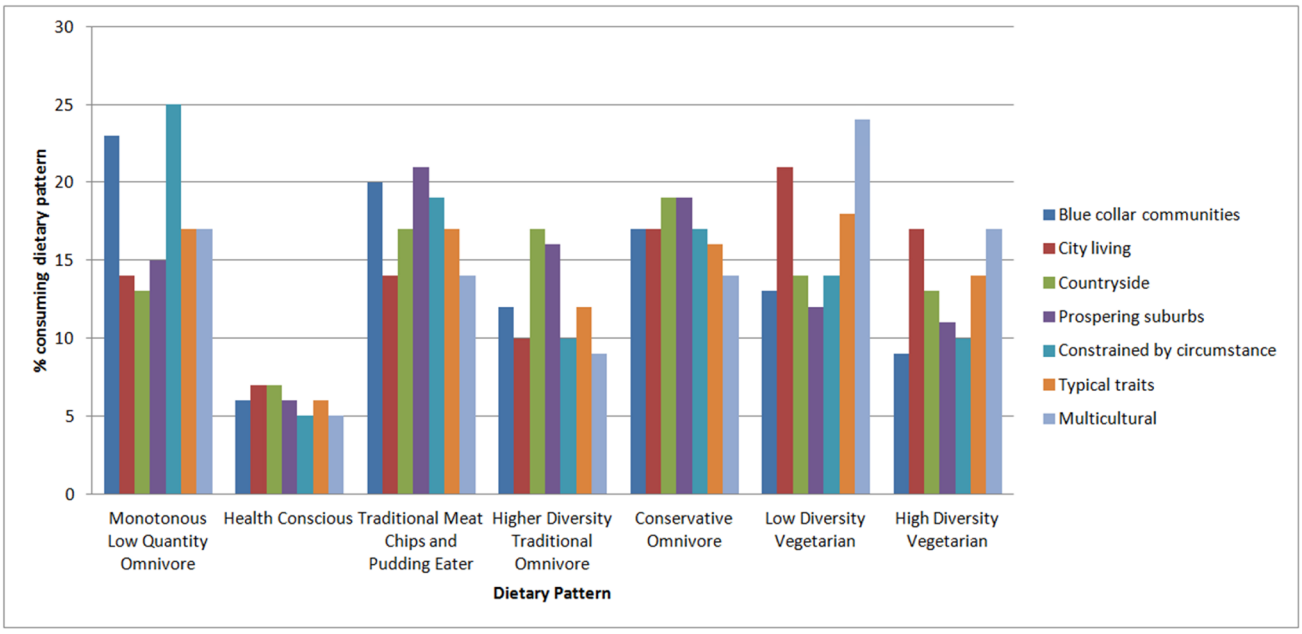


Figure 3: Percentage of UKWCS women consuming each dietary pattern by OAC Supergroup.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

RRR of 1.33 (95% CI 0.11 to 1.59) for consuming the least healthy, "Monotonous Low Quantity Omnivore" dietary pattern whilst also having a significantly lower RRR for consuming the two most healthy dietary patterns, the "Health Conscious" (RRR=0.69 95% CI 0.51 to 0.93) and the "Higher Diversity Traditional Omnivore" (RRR=0.74 95% CI 0.59 to 0.92). The opposite is observed for the 'Countryside' Supergroups who have an increased likelihood of consuming the healthy patterns ("Health Conscious" RRR=1.33 95% CI 1.14 to 1.55 and "High Diversity Traditional Omnivore" RRR=1.37 95% CI 1.21 to 1.54) and decreased likelihood of consuming the unhealthiest, "Monotonous Low Quantity Omnivore" pattern (RRR=0.76 95% CI 0.68 to 0.86).

The adjusted model accounts for total energy intake and physical activity in order that observed effects can be assumed to be dietary pattern related and not due to the volume of energy intake or expenditure. Other variables, such as age, education and social class, which could be considered as confounders have not been adjusted for, as these variables are included in assignment of the OAC.

In the adjusted model, the relationships observed in the unadjusted models are unaffected when additionally adjusting for smoking, total calorie intake including alcohol, typical daily physical activity (METs), age, social class, education. They are in fact accentuated for the "Constrained by Circumstance" group (in comparison to the reference group "Traditional Meat, Chips and Pudding Eaters": "Monotonous Low Quantity Omnivore" diet RRR=1.40 95% CI 1.16 to 1.71, "Health Conscious"

	Monotonous Low Quantity Omnivore	**Health Conscious**	**Traditional Meat Chips and Pudding Eater**	**Higher Diversity Traditional Omnivore**	**Conservative Omnivore**	**Low Diversity Vegetarian**	**High Diversity Vegetarian**
	RRR(95% CI) *p* value	**RRR(95% CI) *p* value**	**Ref.**	**RRR(95% CI) *p* value**	***RRR(95% CI) p value***	**RRR(95% CI) *p* value**	**RRR(95% CI *p* value**
Unadjusted model(pseudo R^2=0.007)							
Blue Collar Communities	1.16(1.00 to 1.36) *p*=0.054	0.87(0.69 to 1.10) *p*=0.206	1.00	0.81(0.68 to 0.97) *p*=0.022	0.87(0.74 to 1.02) *p*=0.095	0.65(0.55 to 0.78) *p*<0.001	0.57(0.47 to 0.69) *p*<0.001
City Living	1.05(0.88 to 1.26) *p*=0.587	1.55(1.23 to 1.95) *p*<0.001	1.00	1.05(0.87 to 1.28) p=0.611	1.36(1.14 to 1.61) *p*=0.001	1.56(1.32 to 1.84) *p*<0.001	1.59(1.33 to 1.89) *p*<0.001
Countryside	0.76(0.68 to 0.86) *p*<0.001	1.33(1.14 to 1.55) *p*<0.001	1.00	1.37(1.21 to 1.54) *p*<0.001	1.15(1.03 to 1.29) *p*=0.016	0.79(0.71 to 0.89) *p*<0.001	0.97(0.86 to 1.09) *p*=0.582
Prospering Suburbs	0.76(0.69 to 0.84) *p*<0.001	0.90(0.78 to 1.04) *p*=0.144	1.00	1.10(0.99 to 1.23) *p*=0.083	0.96(0.87 to 1.06) *p*=0.444	0.59(0.53 to 0.65) *p*<0.001	0.66(0.59 to 0.73) *p*<0.001
Constrained by Circumstance	1.33(0.11 to 1.59) *p*=0.002	0.69(0.51 to 0.93) *p*=0.015	1.00	0.74(0.59 to 0.92) *p*=0.008	0.91(0.75 to 1.10) *p*=0.330	0.71(0.58 to 0.86) *p*=0.001	0.67(0.54 to 0.83) *p*<0.001
Typical Traits	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Multicultural	1.23(1.02 to 1.47) *p*=0.027	1.16(0.90 to 1.49) *p*=0.260	1.00	0.93(0.76 to 1.15) *p*=0.524	1.09(0.91 to 1.32) *p*=0.360	1.70(1.43 to 2.01) *p*<0.001	1.55(1.29 to 1.86) *p*<0.001
Adjusted model(adjusting for smoking, total calorie intake including alcohol and typical daily physical activity(METs)(pseudo R^2=0.10)							
Blue Collar Communities	1.25(1.06 to 1.48) *p*=0.009	0.79(0.62 to 1.00) *p*=0.050	1.00	0.72(0.60 to 0.87) *p*=0.001	0.95(0.80 to 1.12) *p*=0.526	0.70(0.59 to 0.83) *p*<0.001	0.55(0.05) *p*<0.001
City Living	0.88(0.73 to 1.07) *p*=0.208	1.66(1.32 to 2.10) *p*<0.001	1.00	1.10(0.90 to 1.34) *p*=0.349	1.24(1.04 to 1.48) *p*=0.019	1.48(1.25 to 1.75) *p*<0.001	1.64(0.15) *p*<0.001
Countryside	0.79(0.69 to 0.89) *p*<0.001	1.3(1.12 to 1.53) *p*=0.001	1.00	1.35(1.20 to 1.53) *p*<0.001	1.14(1.01 to 1.28) *p*=0.029	0.79(0.70 to 0.89) *p*<0.001	0.95(0.06) *p*=0.386
Prospering Suburbs	0.77(0.69 to 0.86) *p*<0.001	0.91(0.79 to 1.06) *p*=0.215	1.00	1.11(1.00 to 1.25) *p*=0.052	0.94(0.85 to 1.05) *p*=0.259	0.58(0.52 to 0.64) *p*<0.001	0.65(0.04) *p*<0.001
Constrained by Circumstance	1.40(1.16 to 1.71) *p*=0.001	0.66(0.49 to 0.90) *p*=0.008	1.00	0.69(0.55 to 0.86) *p*=0.001	0.98(0.80 to 1.20) *p*=0.859	0.75(0.61 to 0.92) *p*=0.005	0.66(0.08) *p*<0.001
Typical Traits	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Multicultural	0.99(0.82 to 1.21) *p*=0.951	1.24(0.96 to 1.60) *p*=0.107	1.00	0.98(0.79 to 1.21) *p*=0.839	0.99(0.82 to 1.20) *p*=0.938	1.62(1.36 to 1.92) *p*<0.001	1.65(0.15) *p*<0.001

Table 2: Regression models investigating whether OAC Supergroup predicts dietary patterns displaying Relative Risk Ratio (95% Confidence Interval) and *p* value.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

RRR=0.66 95% CI 0.49 to 0.90, "Higher Diversity Traditional Omnivore" RRR=0.69 95% CI 0.55 to 0.86). The 'Blue Collar Communities' also show the same convincing pattern (in comparison to the reference group "Traditional Meat, Chips and Pudding Eaters": "Monotonous Low Quantity Omnivore" diet RRR=1.25 95% CI 1.06 to 1.48, "Health Conscious" RRR=0.79 95% CI 0.62 to 1.0, "Higher Diversity Traditional Omnivore" RRR=0.72 95% CI 0.60 to 0.87).

Interestingly, in both the unadjusted and adjusted models, the 'City Living' and 'Multicultural' Supergroups are approximately 50% more likely to consume a vegetarian diet, with other Supergroups less likely, compared to the reference 'Typical Traits' Supergroup.

The pseudo R^2 value indicates 10% of variation in dietary pattern is explained by the model. This is similar to that shown in the adjusted model using GOR.

DISCUSSION

Variations in dietary pattern consumption are observed both regionally and according to the geodemographic Supergroup in which the women live. These variations occur both within a dietary pattern across the Regions and Supergroups and also between dietary patterns within a Region or Supergroup. Analysis using a geodemographic classification provides more insight into spatial variations in dietary pattern in the UKWCS than analysis using GOR whilst controlling for certain demographic characteristics.

Results suggest an association between a healthy diet – illustrated by the "Health Conscious" dietary pattern and dietary diversity, illustrated by the "Higher Diversity Traditional Omnivore" – and being a member of the more affluent OAC groups. This is supportive of other research suggesting that a healthy diet is more expensive and therefore restricted by financial ability.[24] The Family Spending report from the Living Costs and Food Survey[25] indicates that the OAC Supergroups 'Countryside' and 'Prospering Suburbs' spend the most on food per week, which is also in line with our findings based on the assumption that a healthier diet is a more expensive one.

Unlike earlier studies using fruit and vegetable intake as a proxy measure of a healthy diet,[12] in this study the "Health Conscious" dietary pattern incorporates more dietary components than just fruit and vegetable intake to represent dietary healthiness. A full spectrum of dietary diversity is also represented by the dietary patterns (as indicated by the pattern names). High dietary diversity appears to be associated with living in more affluent OAC Groups, and conversely dietary monotony correlates with the poorer areas. A conservative dietary pattern and the traditional dietary pattern have slightly higher concentrations in the deprived areas.

Summary characteristics for the UKWCS vary little by region from the mean values for the cohort as a whole. However, when the same characteristics are presented by OAC Supergroup variation is greater. The OAC uses variables such as age, occupation and education, as collected in the census. No information relating to diet is included in the census or the OAC, yet increased variation in dietary patterns by OAC rather than GOR is observed supporting evidence that socio-demographic characteristics influence diet,[26] but also that small area geography – the immediate local environment – influences diet.[27] Using the small geographic unit of Output Area (containing approximately 250 individuals) compared to the large geographical unit of a GOR (containing millions of individuals) produces results which will be much more relevant at a local area level.

STRENGTHS AND LIMITATIONS

The UKWCS, specifically designed to investigate the effect of dietary patterns on health outcomes, provides quality dietary data for analysis. Vegetarians were deliberately over sampled and as such make up a higher proportion in this cohort than in the general population. This means that this study is powered sufficiently to detect differences between different types of diet which is a strength of the design. Measurement of diet is subject to a range of potential bias including under or over reporting. Collecting information from a sample which is large enough to be generalisable to a given population is also challenging due to temporal and financial constraints, making this study a valuable resource.

Geographic location of participants was not a design factor for the UKWCS, so despite large numbers in each of the nine GORs of the England and Scotland and Wales these regions are not equally represented across the cohort. The lowest numbers (n=957) were observed residing in the North East. However, when considering this in the context of other dietary survey information, this is a large number of women on which to base robust analysis. The National Diet and Nutrition Survey (NDNS), for example, whilst it was designed to be geographically representative, only includes 3073 individuals in total (from the three year rollout) of which only about one quarter are women. The UKWCS sample is approximately 40 times the size of that national sample of women.

Recruitment of the UKWCS was on a volunteer basis from a WCRF mailing list of previous questionnaire participants so it may be expected that there is some volunteer bias. The women are predominantly middle age, middle class and white. This may account for the over representation observed when comparing the UKWCS to the whole UK population, in the 'Countryside' and 'Prospering Suburbs' Supergroups which are characterised by middle age, more middle class, white individuals with larger detached houses. Under representation is observed in 'Blue Collar Communities', 'Constrained by Circumstance' and 'Multicultural' Supergroups. Despite this there are large numbers of women in each of the seven OAC Supergroups, sufficient to provide confidence in the associations observed in this study.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

The dietary patterns used, whilst data driven, are not necessarily comparable to dietary patterns used in other surveys. That said, they provide a comprehensive illustration of dietary patterns consumed in the UK. Comparing these to another data driven but not international classification, such as the OAC could be considered subjective, but this paper illustrates how different spatial measures can be useful in public health and specifically dietary research, rather than critique dietary patterns or geodemographic classifications.

For some geodemographic classifications, created by market research companies, the methods used to generate the classification are not transparent as these are the intellectual property of the company. This can be a limitation for use in research as it can make adjustment for confounding a guessing game. However, the methods used to generate the OAC are reported in full, allowing for researchers to have clear insight into the classification data they are using.

The OAC groups include all of the UK population who completed the Census questionnaire, so incorporate men and children in addition to women. Whilst the NDNS reports statistical differences between the food consumed by men and women (stratified both by region and whether or not the individuals are in receipt of benefits)[28] it has not specifically reported whether there was a difference in the diets of men and women within the same household in the UK. With this in mind, the results of this study can only reliably be applied to women.

The dietary data used in this study were collected in the late 1990s. It is feasible that dietary habits could have changed since this time. However it is rare that dietary information of this quality is collected in such a large sample in the UK. Prospective dietary data collection is essential when considering influence on diseases with a latent development period, such as cancer. Collection dietary records for cancer cases can impact on subject recall of their diet.[2] Therefore the application of these results with respect to the effect of diet on health is relevant, despite possible dietary change since the data was collected.

This study uses the UK as a case study. However, the methods are transferable elsewhere and it would be possible to carry out the same sort of analysis for other countries for which geodemographic classifications have been generated. An example, Callcredit group have generated geodemographic classifications for 40 countries worldwide.[29]

POLICY IMPLICATIONS

Dietary pattern variation between regions, with the exception of the "Health Conscious" dietary pattern (p=0.186), is statistically significant (p<0.01). Such variation at a large geographical scale is suggestive that there are regional influences on eating habits, not just that of the local surrounding area. Further investigation could be carried out into this regional variation; however, it may be erroneous to ascribe specific factors to a particular region, if certain areas within that region have a dominating influence on the dietary pattern. The regression analysis using region, including demographic variables, shows that some regions have significant RRRs of consuming a particular dietary pattern. For example Greater London has significantly increased risk, compared to those living in the South East, of consuming both the "Health Conscious" (most healthy) and the "Monotonous Low Quantity Omnivore" (least healthy) diet (compared to consuming the traditional diet). Observations like this mean that implementing a cost effective nutritional intervention at the regional level would be extremely difficult.

However, when we consider dietary pattern variation by geodemographic Supergroup the results present a clearer picture. Those living in a 'Blue Collar Community', for example have significantly increased risk of consuming the "Monotonous Low Quantity Omnivore" (least healthy) dietary pattern and a significantly reduced risk of consuming the "Health Conscious" and "High Diversity Traditional Omnivore" (two most healthy) dietary patterns, suggesting that it would be worthwhile implementing a healthy diet promotion in these types of areas. The regional regression model, controlling for age and education does not produce such clear results and the regression models using geodemographic Supergroups, indicating that the small scale geography combined with a number of demographic variables is a powerful tool. Combination of both the regional and Supergroup results could help to target interventions to certain types of areas within the region most at risk of consuming a poor dietary pattern.

Being able to estimate dietary patterns at a small area level using a classification such as OAC, allows for smarter targeting of public health interventions, to improve diet and subsequent health. For example, to provide a specific intervention to individuals to living in 'Constrained by Circumstances' Supergroup (who consume the highest percentage of "Monotonous Low Quantity Omnivore" diets) which would encourage them to introduce more variety into their diets with the best addition being fruit and vegetables. This could be done through social services interventions in specific communities, or at a GP practice level in local communities.

FURTHER WORK

Future studies could investigate how consuming each of these dietary patterns could influence long term health, which would strengthen the relevance of this research to public health interventions. Another step would be to incorporate the cost of these dietary patterns in order to assess the economic influence of food price, compared to usage by geodemographic type. It would be key to profile the dietary patterns of this cohort for cities in the UK using a geodemographic classification and investigate patterns observed. Additional case studies from other countries would allow for international comparisons to be made.

CONCLUSION

Dietary pattern consumption is associated with where

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

individuals reside. The type of area, using a small scale geographical unit, combined with demographic characteristics provides richer prediction of dietary consumption than the large regional unit. Healthy or diverse dietary patterns are more common in geodemographic groups in the 'Countryside' or 'Prospering Suburbs' with less healthy patterns in areas such as 'Constrained by Circumstance' and 'Blue Collar Communities'. With this in mind it may be beneficial to use such classifications in the application of dietary advice to encourage healthy eating in order to promote long term health. Geodemographic classifications are a useful tool to better understand spatial variations in diet in the UK.

DATA SHARING STATEMENT

Further information on the UK Women's Cohort Study Data is available at www.ukwcs.leeds.ac.uk

ACKNOWLEDGEMENTS

The main author was funded through and ESRC/MRC PhD studentship. The UKWCS was initially established using funding from the World Cancer Research Fund. Thanks to Dr. Lorna Fraser for advice with the regression analysis.

CONFLICTS OF INTEREST: None.

CONSENT STATEMENT

The study in the article has 35,000 participants who consented at the time of recruitment to the cohort in the 1990s, as described in the methods. In line with this consent, no personally identified information is included in this article.

REFERENCES

1. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*. 1981; 66: 1191-1308. doi: 10.1093/jnci/66.6.1192

2. Key T, Allen N, Spencer E, Travis R. The effect of diet on risk of cancer. *Lancet*. 2002; 360: 861-868. doi: 10.1016/S0140-6736(02)09958-0

3. The National Archives. Department of Health. Foresight - Tackling Obesities: Future Choices – Project report. Obesity: Healthy Weight, Healthy Lives. Web site. http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publichealth/Healthimprovement/Obesity/DH_079713. Updated October 19, 2007. Accessed January 5, 2016.

4. Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. *Public Health Nutr*. 2002; 5: 645-654. doi: 10.1079/PHN2002332

5. Sofi F, Cesari F, Abbate R, Gensini G, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ*. 2008; 337. doi: 10.1136/bmj.a1344

6. Trichopoulou A, Vasilopoulou E. Mediterranean diet and longevity. *Br J Nutr*. 2000; 84 Suppl 2: S205-S209.

7. Greenwood DC, Cade JE, Draper A, Barrett JH, Calvert C, Greenhalgh A. Seven unique food consumption patterns identified among women in the UK Women's Cohort Study. *Eur J Clin Nutr*. 2000; 54(4): 314-320.

8. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet*. 2011; 378: 804-814. doi: 10.1016/S0140-6736(11)60813-1

9. Monsivais P, McLain J, Drewnowski A. The rising disparity in the price of healthful foods: 2004–2008. *Food Policy*. 2010; 35: 514-520. doi: 10.1016/j.foodpol.2010.06.004

10. Drewnowski A, Monsivais P, Maillot M, Darmon N. Low-energy-density diets are associated with higher diet quality and higher diet costs in French adults. *J Am Diet Assoc*. 2007; 107: 1028-1032. doi: 10.1016/j.jada.2007.03.013

11. Cummins S. Food environments and obesity--neighbourhood or nation? *Int J Epidemiol*. 2005; 35: 100-104. doi: 10.1093/ije/dyi276

12. Wrigley N, Warm D, Margetts B, Whelan A. Assessing the Impact of Improved Retail Access on Diet in a 'Food Desert': A Preliminary Report. *Urban Stud*. 2002; 39: 2061-2082. doi: 10.1080/0042098022000011362

13. Olsen JA, ed. Principles in Health Economics and Policy. Oxford, UK: Oxford University Press; 2009.

14. Bronfenbrenner U. Toward an Experimental Ecology of Human Development. *American Psychologist*. 1977; 32: 513-531. doi: 10.1037/0003-066X.32.7.513

15. Gibney MJ, Margetts BM, Kearney JM, eds. Public Health Nutrition. 5th ed. Oxford, UK: Blackwell Science Ltd; 2004.

16. Cade JE, Burley VJ, Alwan N, et al. Cohort profile: the UK Women's Cohort Study (UKWCS). *Int J Epidemiol*. 2015; pii: dyv173. doi: 10.1093/ije/dyv173

17. Cade JE, Burley VJ, Greenwood DC, Group UKWsCSS: The UK Women's Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutr*. 2004; 7: 871-878.

18. Woodhouse A, Calvert C, Cade J. The UK Women's Cohort Study: background and obtaining local ethical approval. *Proc Nutr Soc*. 1997; 56: 64A.

19. Morris MA, Hulme C, Clarke GP, Edwards KL, Cade JE.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

What is the cost of a healthy diet? Using diet data from the UK Women's Cohort Study. *J Epidemiol Community Health*. 2014; 68: 1043-1049. doi: 10.1136/jech-2014-204039

20. Vickers D, Rees P, Birkin M. Creating the national classification of census output areas: data, methods and results. http://eprints.whiterose.ac.uk/5003/1/05-2.pdf. Working Paper 05/2; School of Geography, University of Leeds, Leeds, UK. Published December 22, 2008. Updated June 4, 2014. Accessed January 5, 2016.

21. UK Data Service Census Support. GeoConvert. Web site. http://geoconvert.mimas.ac.uk/. Accessed January 5, 2016.

22. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000; 32(9 Suppl): S498-S504.

23. *STATA IC 12.1*. (for Windows) [computer program]. Version 2.1. College Station TSL ed.: Statacorp; 2012.

24. Maillot M, Darmon N, Vieux F, Drewnowski A. Low energy density and high nutritional quality are each associated with higher diet costs in French adults. *Am J Clin Nutr*. 2007; 86: 690-696. http://ajcn.nutrition.org/content/86/3/690.full.pdf. Accessed January 4, 2016.

25. Office for National Statistics. Family Spending - A report on the 2009 Living Costs and Food Survey. The National Archives. http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/rel/family-spending/family-spending/2010-edition/index.html. Published November 30, 2010. Updated November 29, 2011. Accessed January 4, 2016.

26. Aggarwal A, Monsivais P, Cook AJ, Drewnowski A. Does diet cost mediate the relation between socioeconomic position and diet quality? *European Journal of Clinical Nutrition*. 2011; 65: 1059-1066. doi: 10.1038/ejcn.2011.72

27. Fraser LK, Edwards KL. The association between the geography of fast food outlets and childhood obesity rates in Leeds, UK. *Health Place*. 2010; 16: 1124-1128. doi: 10.1016/j.healthplace.2010.07.003

28. Food Standards Agency, Department of Health. National Diet & Nutrition Survey: adults aged 19 to 64 years. The National Archives. 2002; 1. Web site. http://tna.europarchive.org/20110116113217/http://www.food.gov.uk/science/dietarysurveys/ndnsdocuments/ndnspreviousurveyreports. Accessed January 4, 2016.

29. Callcredit Information Group. Customer segmentation & analysis for the UK & key global markets. Web site. http://www.callcredit.co.uk/products-and-services/consumer-marketing-data/segmentation-analysis. Accessed January 4, 2016.

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

APPENDIX

Appendix A – Summary of dietary patterns

Dietary pattern	High quantities	Moderate quantities	Low quantities
Monotonous Low Quantity Omnivore	White bread, milk, sugar	Potatoes, meat	Most other foods
Traditional Meat, Chips and Pudding Eater	White bread, chips, meat, sugar, high-fat and creamy food, biscuits, cakes	Most other foods	Wholemeal food, soya products, vegetables, salad, fruit
Conservative Omnivore	-	Most food, including potatoes, meat, fish, eggs, fruit, vegetables	Cereals, chips, wholemeal food, nuts, pulses, spreads and dressings, chocolate, crisps, biscuits. Less red meat, less chips and less puddings than the Traditional Meat Chips and Pudding Eater and the Higher Diversity Traditional Omnivore.
Low Diversity Vegetarian	Wholemeal bread, soya products, pulses, fruits (not exotic fruit), vegetables.	Cereals	Butter, eggs, meat, fish
Higher Diversity Traditional Omnivore	Chips, white pasta and rice, high-fat and creamy food, eggs, meat, fish, chocolate, biscuits, crisps. More fish and salad and general diversity than the Traditional Meat Chips and Pudding Eater.	Vegetables, fruit and alcohol.	Less cakes and puddings than the Traditional Meat Chips and Pudding Eater.
High Diversity Vegetarian	Wholemeal bread, cereals, wholemeal pasta and rice, soya products, spreads, nuts, pulses, vegetables, fruit, herbal tea (generally higher consumption of these products that the Low Diversity Vegetarian).	-	White bread, meat, fish
Health Conscious	Bran, potatoes, wholemeal food, yoghurt, low-fat dairy products, pulses, fish, vegetables, salad, fruit	Most other foods	Chips, sugar

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-104

Appendix B – Summary of OAC Supergroups

Supergroup	Distinctive variables - High	Distinctive variables - Low
1 - Blue Collar Communities	Age 5-14 Lone parent households Households with non-dependent children Terraced housing Routine/Semi-routine employment Mining/Quarrying/Construction employment Manufacturing employment Retail trade employment	Indian, Pakistani and Bangladeshi Black Born outside the UK Rent (Private) Flats Higher education qualifications Financial intermediation employment
2 - City Living	Age 25-44 Born outside the UK Population density Single person household Rent (private) Flats No central heating Higher education qualification Students Financial intermediation employment	Ages 0-4,5-14,25-44 and 65+ Single parent household Households with non-dependent children Rooms per household Provide unpaid care Economically inactive/looking after family General employment
3 - Countryside	Ages 45-64 and 65+ Detached housing Rooms per household 2+car households Work from home Provide unpaid care Agricultural employment	Indian, Pakistani and Bangladeshi Black Population density Single person household Flats People per room Public transport to work Unemployment
4 - Prospering Suburbs	Age 45-64 Two adults no children Households with non-dependent children Detached housing Rooms per household 2+car households Provide unpaid care	Indian, Pakistani and Bangladeshi Black Divorced/separated Single person household Single pensioner households Renting public and private Terraced housing Flats No central heating Limiting long-term Illness Unemployment
5 - Constrained by Circumstance	Age 65+ Divorced/separated Single pensioner households Lone parent households Rent (Public) Flats People per room Routine/Semi routine employment Limiting long-term Illness Unemployment	Two adults no children Rent (Private) Detached housing Rooms per household Higher education qualification 2+ car households Work from home
6 - Typical Traits	Work part time Terraced housing	Age 65+ Rent (Public)
7 - Multicultural	Ages 0-4 and 5-15 Indian, Pakistani and Bangladeshi Black Born outside the UK Population density No central heating People per room Public transport to work Students Unemployment	Ages 45-64 and 65+ Single pensioner households Two adults no children Economically inactive/looking after family or home

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-105

Research

*Corresponding author
Abdulmumini Usman, MD
WHO Representative (WR)
World Health Organisation Country Office
Juba, South Sudan
Tel. +211955026052
E-mail: usmanaeri@yahoo.com

Volume 1 : Issue 1
Article Ref. #: 1000EPOJ1105

Article History
Received: February 8th, 2016
Accepted: March 28th, 2016
Published: March 28th, 2016

Citation
Boateng K, Usman A, Laku A, Mostafah Y, Bimpa DD, Baba S. Targeted measles outbreak response vaccination in the context of measles control and elimination: Experiences from South Sudan. *Epidemiol Open J*. 2016; 1(1): 33-39. doi: 10.17140/EPOJ-1-105

Targeted Measles Outbreak Response Vaccination in the Context of Measles Control and Elimination: Experiences from South Sudan

Kofi Boateng, MS[1]; Abdulmumini Usman, MD[1*]; Anthony Laku, MD[2]; Yehia Mostafah, MD[1]; Dieu Donne Bimpa, MD[1]; Sampson Baba, MD[2]

[1]World Health Organisation Country Office, Juba, South Sudan
[2]Directorate of Primary Health Care, Ministry of Health, Juba, South Sudan

ABSTRACT

Introduction: Measles elimination interventions in South Sudan have relied on mass campaigns due to reoccurring humanitarian crisis over decades. This paper examines the effects of targeted measles vaccinations on efforts at eliminating measles in the country.
Methods: Time trend and an analytical cross-sectional design were applied on South Sudan Measles case-based surveillance dataset 2011-2015. Logistic regression of IgM positive cases against vaccination status and adjusted for age and unknown vaccination status were used to determine the likelihood of reduced risk of measles at 95% CI.
Results: Routine immunization, follow-up and outbreak response coverage for measles vaccination over the period were sub-optimal. Even though the proportion of confirmed measles cases among vaccinated population was irregular ranging 14.2% to 61.9% within the period reviewed, measles vaccination generally reduced the risk of the disease in the population by 30% (odds 0.7, 95% CI 0.4, 1.0) from 2011-2015. A trend analysis showed that the likelihood of reduction of measles burden varied per year, but a higher reduction of risk was observed in 2015 (odds 0.05 (95% CI <0.01, 0.35) preceded by follow-up campaigns. Adjusting for age and unknown vaccination status, there were no statistically significant difference for the trends of odds, however the significant decrease in odds in 2015 (OR 0.01 (95% CI [0.01, 0.35]) R^2 0.45) is due to a unit change in age.
Conclusions: Targeted measles outbreak vaccinations generally reduce the burden of measles however the extent of reduction is more reflected in a year following a mass measles campaign as compared to outbreak response vaccination. Thus measles follow-up campaigns are necessary for sustained measles control and elimination.

KEYWORDS: Measles; Outbreak; World Health Organization (WHO); Vaccination; South Sudan.

INTRODUCTION

Measles continues to cause death and severe complications including pneumonia, croup, encephalitis, blindness and otitis media in children and it remains one of the most important causes of child morbidity and mortality globally.[1] Following an infection, the virus can persist for a long time in the body contributing to the development of lifelong immunity.[2] According to the World Health Organization (WHO),[3] measles can be prevented readily by vaccination, reaching and maintaining high immunization coverage in a population. Thus the organization recommends immunization against measles for all susceptible children and adults for whom measles vaccination is not contraindicated in order to reach and maintain a population herd immunity of at least 90% in all second administrative levels, a prerequisite for prevention of measles epidemics. In addition, the World Health Organization (WHO) recommends two doses of measles for all children with the first dose in infancy and the second dose may occur

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-105

either at a scheduled age through routine services or periodically through Supplementary Immunization Activities (SIAs) or mass campaigns targeting at least 95% coverage. The organization has also developed the Measles Strategic Planning (MSP) tool to harness routinely available data to estimate effectiveness and cost effectiveness of vaccination strategies.[4] The vision of the Global measles and rubella strategic plan: 2012-2020[5] is to achieve and maintain a world without measles, rubella and Congenital Rubella Syndrome (CRS) or measles eradication is defined as the world-wide interruption of transmission of the virus, and represents the sum of successful elimination efforts in all countries and regions.[6]

South Sudan revitalized measles programme after the Comprehensive Peace Agreement (CPA) in 2005 with a catch-up campaign conducted in 2005-2007 recording post campaign evaluation coverage of 74%. The catch-up campaign was followed by Accelerated Child Survival Initiatives (ACSI) in 2009 and a follow-up campaign in 2012 which recorded administrative coverage of 62% and 92% respectively. The country's measles elimination strategy from 2014-2020 was developed in 2013 which sets out objectives in line with the regional and global strategic goals. In April 2014, another follow-up campaign was implemented in seven states, and partially in 25 counties in the three conflicts affected states of Jonglei, Unity and Upper Nile. However, over the period of 2005-2015, laboratory confirmed measles outbreaks occur every year, and are responded to with selective vaccination with limited geographic scope usually within the affected county or its entirety but not in bordering counties at risk. Routine immunization is mostly conducted by NGOs, yet it is limited to the functional heath facilities of which an estimated 32% provide mainly fixed vaccination services. Since 44% of the population have access to functioning health facilities, the Ministry of Health (MoH) with the support of partners conducts three rounds of outreach sessions in a campaign mode in a year. The conflict that started in December 2013 limits access to vaccination campaigns. Thus, the current measles vaccination programme is limited to routine vaccination mostly implemented at functional health facilities and outbreak campaign response. Surveillance remains largely passive under the Integrated Disease Surveillance and Response system currently under development. However, a Case-based surveillance was established in October 2011 in a parallel mode setting the stage for the elimination agenda.

Even though routine immunization is known to be the cornerstone in eliminating vaccine preventable diseases such as measles, fragile routine immunization system coupled with the complexity of emergencies in the context of South Sudan have led to reliance on mass campaigns to reach elimination targets. However, the effectiveness of follow-up campaigns as compared with outbreak responses in reducing the burden of measles in the population remains uncertain. The aim of this study is to determine the effectiveness of the targeted measles outbreak vaccinations currently practiced in South Sudan for measles elimination.

METHODS

We used time trend analysis of secondary data sources for routine and supplementary measles vaccination, and an analytical cross-sectional design on the dataset of case-based surveillance on measles in South Sudan from 2011-September 2015 to examine the risk of measles in the population over the period.

The exposure factor was evidence of history of vaccination against the outcome of IgM test results for measles.

Data Sources

The WHO/Unicef Joint Report estimates for 2011, 2013-2014, Expanded Programme on Immunization (EPI) Coverage Survey for 2012, and Administrative data source for 2015 were used for routine immunization coverage for measles. Supplementary Immunization data were sourced from reports from measles follow-up, preventive and outbreaks vaccination campaigns over the period 2011-2015.

The centralized measles case-based surveillance database hold investigated measles cases from all reporting health facilities. Data on measles cases are captured on a generic IDSR case-based form containing all relevant variables: epidemiological numbers, age, sex, residence, and date of onset of rash as well as date and doses of previous vaccinations, dates of notification, and results of samples. The database is on Microsoft Access Database (mdb) platform designed with Epi Info 3.5.0.

Serology

Whole blood venipuncture specimens were obtained from suspected measles cases in health facilities, kept unfrozen at 4-8 ˚C for 24 hours until complete retraction of clot and serum is separated or; allowed to clot and centrifuged at 100 g for 10 minutes to separate the serum. The separated serum was transferred into serum tubes and stored at 20 ˚C until transported in a specimen carrier with ice packs, to the National Public Health Reference Laboratory and kept at 20 ˚C until tested. WHO validated Dade Behring kits were used to perform measles indirect IgM test.

Measles cases were defined by laboratory confirmation of IgM presence for measles.

Data Analysis

We mapped the measles routine immunization and SIA coverage data over the years 2011-2015. The measles line list was extracted from the Measles Case based dataset and analyzed using EPI info version 7 and Statistical Package for Social Sciences (SPSS) version 20. Data were cleaned and validated with reference to filed hard copies of the case investigation forms.

We excluded cases without serum samples, as well as

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-105

cases with samples but with date of previous measles vaccination within 28 days before onset of rash. In addition, epidemiologically linked and compatible cases were also excluded in the analysis in terms of comparing with IgM negative cases in order to control bias resulting from discretional definition of such cases.

The trends of measles cases were mapped with types of measles SIAs over time in an epidemiological curve. Cases with evidence of vaccination and IgM +ve test results for measles were recorded 1 and the absence of both variables, 0. Measles cases with evidence of no history of vaccination were used as referent and binary logistic analysis used to estimate the odds of measles IgM +ve cases accounting for variability at 95% confidence interval for each year. Interactive logistic regression was also applied to adjust separately for influences of age and cases with serum samples but with unknown vaccination status on the odds ratio of measles among vaccinated population over time. Estimates of odds and Mcffaden's pseudo–R square were made. The analysis to some extent controlled for the effects of recall or investigation biases that informed records on vaccination status, but absence of data on corresponding vaccination intervention to doses as well as co-morbidity were limitations hence, uncontrolled and therefore limited estimation of vaccine effectiveness. Notwithstanding, the assumption made was that vaccination doses where largely related to major interventions (follow-up campaigns or outbreak response vaccinations) within the year.

RESULTS

The WHO and UNICEF joint estimate puts routine immunization coverage for third dose Diphtheria Pertussis Tetanus (DPT3) at 60.0%, 65.0% and 47.0% for 2011, 2013 and 2014 respectively. The EPI Coverage survey in 2012 estimated DPT3 coverage of 45.9%. The administrative coverage for routine immunization in 2015 was 52.1%.

Administrative coverages of selective measles outbreak response vaccinations in 2011 and 2013 were 92.0% and 90.2% respectively. Post campaign coverage survey after the Follow-up campaigns conducted in 2012 and 2014 recorded 92.8% by figure mark and 88.0% evidenced by card respectively (Table 1).

Out of the 1087 suspected measles cases investigated from 2011-2015, 436 had evidence of known vaccination status, of which 291 representing 66.7% (95% CI 62.8-71.1) had received no dose of measles vaccine as against 145, forming 33.3% (95% CI 28.9, 37.9) with evidence of receipt of a dose or more (Figure 1).

Of the total cases investigated, 629 (57.9% (95% CI 54.8, 60.8) were laboratory confirmed measles cases and 458 (42.1%) discarded as non-measles cases as shown in Figure 2. However of the 436 cases with evidence of known vaccination status, 62.1% (95% CI 57.4, 66.7) were lab confirmed measles cases (Immunoglobulin M (IgM) positive), and the rest, 37.8% (95% CI 33.3, 42.6) non measles cases (IgM negative) (Figure 2).

Measles cases have multiple peaks in a year. In 2013, peaks were observed in January with 11 cases, 32 cases in May and 18 cases in October. In 2012 four peaks were observed in February (17 cases), May (18 cases) October (15 cases) and 8 cases in December. In 2013 the first peak of 8 cases in January rose sharply to 48 cases in May and declined to 15 cases in October. In the same year, 2013 cases were not reported in November and December. The three peaks in 2014 were recorded in

Year	Routine Immunization (%)	Supplementary Immunization Activities (%)
2011	60.0[b]	92.0
2012	45.9[a]	92.8[c]
2013	65.0[b]	90.2
2014	47.0[b]	88.0[c]
2015	52.1[d]	

[a]*EPI Coverage Survey (2011)*
[b]*Joint WHO UNICEF estimate*
[c]*PCE Coverage from F-up campaign*
[d]*Annualised Routine Immunization*

Table 1: Routine immunization coverage and SIAs.

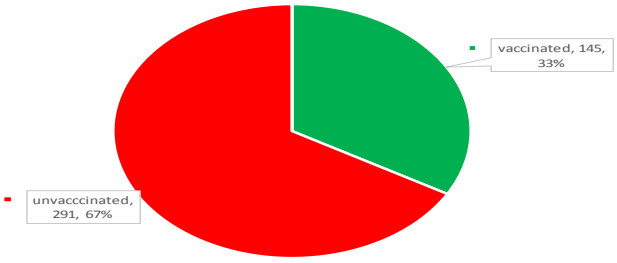


Figure 1: Proportional distribution of vaccination status of investigated measles cases 2011-2015, South Sudan (n=436).

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-105

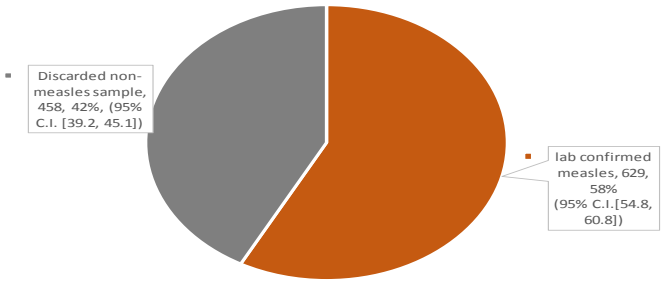


Figure 2: Proportional distribution of laboratory result of investigated measles cases, 2011-2015, South Sudan.

January (12 cases), March 26 cases and 36 cases in November. In 2015 a sharp rise of cases were noted in March (12 cases) but declined to 2 cases in August as detailed in Figure 3.

The proportion of confirmed measles cases with history of vaccination decreased from 24.3% in 2011 to 14.2% in 2012 but with a sharp rise to 61.9% in 2014 and a drop to 21.4% in 2015 as shown in Table 1 below. Even though measles vaccination reduced the risk of the disease by 30% (odds 0.7; 95% CI 0.4-1.0) from 2011-2015, a trend analysis showed that the likelihood of reduction of measles burden due to measles vaccination varied per year, but a higher reduction of risk were observed in years (2012 (odds 1.06 (95% CI 0.32-3.55) and 2015 (odds 0.05 (95% CI <0.01-0.35) preceded by follow-up campaigns (Table 2).

Adjusting for samples with unknown vaccination status, the odds of measles among samples with known vaccination status increased in 2012 and 2013 but sharply dropped in 2014 to 2015. The decrease in 2012 and 2014 cannot be explained by the vaccination, however in 2015, 45% of the unit change of reduced risk to measles infection can be explained by the vaccination status of the sample (OR 0.01 (95% CI 0.01-0.35) R^2 is 0.45) (Table 3).

The level of likelihood of reduction of measles in the vaccinated population when adjusted for age was generally less

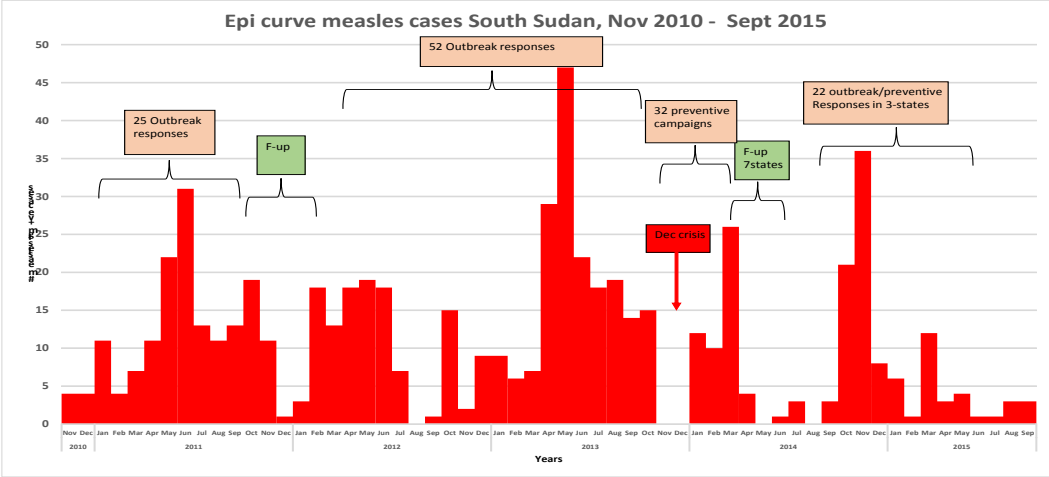


Figure 3: Epi curve of measles cases with history of vaccination 2010-2015.

Year	Total number IgM +ve	Vaccinated		
		% IgM +ve	Odds	95% CI
2011-2015	145	29.9	0.70	0.4, 1.0
2011	74	24.3	1.99	0.67, 5.88
2012	56	14.2	1.06	0.32, 3.55
2013	85	30.5	1.45	0.55, 4.02
2014	42	61.9	0.81	0.32, 2.02
2015	14	21.4	0.05	0.00, 0.35

Table 2: Trend analysis of odds of measles cases among vaccinated population.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-105

Year	OR adjusted for unknown vaccination status		OR adjusted for age	
	OR [95% CI]	R^2	OR (95% CI]	R^2
2011	0.6 [0.30, 1.56]	0.09	0.90 [0.81, 0.95]*	0.10
2012	1.1 [0.30, 3.51]	0.00	0.90 [0.80, 1.00]	0.04
2013	1.5 [0.51, 3.80]	0.08	1.01 [0.91, 1.12]	0.19
2014	0.8 [0.30, 2.10]	0.00	0.99[0.94, 1.04]	0.00
2015	0.01 [0.01, 0.35]*	0.45	0.98 [0.71, 1.23]	0.47

*p<0.05

Table 3: Odds of IgM +ve per year adjusted of unknown vaccination status and age.

than 10% from 2011-2012. A higher percentage of the phenomenon in 2013 (19%) and 2015 (45%) could be explained by a unit change of age of the population, however in 2014 the unequivocal risk of measles between vaccinated and unvaccinated population cannot be explained by the age between the groups (R^2=0.00). This notwithstanding there is no significant difference between the levels of likelihood of reduction of measles among the vaccinated population from 2011 to 2012.

DISCUSSIONS

Globally measles control and elimination strategies have made tremendous impact on childhood morbidity and mortality.[3,4] Optimum benefits are achieved following high quality and high coverage through routine immunization, follow-up campaigns and outbreak vaccinations as well as effective case management integrated with appropriate administration of doses of Vitamin A.[3] Sustained high routine immunization coverage for 1st and 2nd doses of Measles Containing Vaccines (MCV) is known to enhance population herd immunity of children thereby reducing levels of population susceptibility.[4,6] South Sudan measles elimination strategy which was preceded by a control strategy during the 2005 CPA period formed the foundation of formalizing EPI structures which was underdeveloped and therefore, has remain very fragile with sub-optimal outcomes. The two years phased catch-up campaign in 2005-2007 in addition to the accelerated child survival intervention in 2009 recorded below 70% coverage. Yet, gains could not be sustained in the context of the weak routine immunization system which recorded estimates below 70% at both national and sub-national levels since 2011 to 2015. The low performance may also be accounted for by the multiple populations mix following the 2011 independence resulting in 2.7 million influx of returnees and refugees from neighboring countries thereby raising susceptibility levels and precipitating rapid transmission of the virus which has been further worsened by the crisis in December 2013 that has caused the displacement of over 1.6 million people.[6] The record of low coverage for measles intervention in deprived settings and the resurgence of measles outbreaks have been recorded in parts of Africa and parts of East Asia[7,8] reaffirming the need for strengthened health systems for disease control and elimination.

Measles follow-up campaign provides opportunity to reduce high levels of susceptible population and further enhance herd immunity through the provision of opportunity for a second MCV dose.[2,9] The acceptable coverage for measles follow-up campaigns is at least 95% preferably verified by card following which period of outbreaks lengthens for 1-3years and frequency reduced.[6] During outbreaks selective vaccination coupled with enhanced routine immunization and active surveillance are recommended.[1,4,6] In this study, follow up campaigns in South Sudan usually were preceded by an average of 20 lab confirmed outbreak response vaccinations per year and was conducted in 2 years interval. SIAs coverages were however sub-optimal due to multiplicity of systemic factors including limited number of qualified persons to administer the vaccine, barriers in terms of geographic access as well as limited capacities of implementing partners. Additional barriers were limited cold chain infrastructure and inadequate management of existing ones to ensure vaccine efficacy both in routine and follow-up campaigns. All follow-up campaigns were therefore phased, allowing for high number of missed target population. Consequently, the trend of peaks of measles cases, affirm the short interval of build-up of susceptibles. Similar trends have been observed in many difficult settings in Africa and South America were follow-up campaigns and intervals of resurgence of multiple outbreaks occurred in less than 2 years.[10,11] Implementation of high quality follow-up campaigns in low resourced settings therefore remains a challenge.

Measles vaccine is cost effective in mitigating the burden of the disease,[1,6,12,13] however it is among the most heat sensitive vaccines. Incidences of measles have seen a drastic decline as evidenced in many settings including developing countries.[5,14] It is established that approximately 85% and 95% of population receiving measles first and second dose respectively could reach optimum seroconversion rates against the disease.[6,14,15] South Sudan has an open vial policy for measles. Our findings showed that in South Sudan, high percentage (29.9% (95% CI 22.5, 37.4) of measles cases with history of previous doses of MCV were laboratory confirmed discounting for MCV doses given within 28 days before onset of rash. We also observed that yearly trends of proportions of laboratory confirmed measles cases among vaccinated cases peaked in years were outbreak vaccinations were conducted but reduced in years following follow-up campaigns. The high percentage of measles cases among the vaccinated population could be attributed to vaccine failure due to poor cold chain, vaccine handling and administrative practices, noting the weak infrastructure and human resources capacities in the country. In recent times, similar factors have accounted

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-105

for the occurrence of outbreaks in both developing and underdeveloped countries.[10,11,16-19] Comparing the risk of measles among vaccinated population over time was limited by possible recall bias since vaccination status of cases was not evidenced by card and detailed history of vaccine handling. Therefore, the extent of variation of trends that could be attributed to vaccine failure may be deficient but possibly cannot be discounted considering the weak health system.

The burden of mortality and morbidity due to measles and accompanying socio-economic cost have been well acknowledged globally to have declined significantly through vaccinations.[5,12,18] In this study, we found that from 2011-2015 a unit change of doses of measles vaccines administered into the population reduced the risk of measles by 30%. A yearly analysis however indicated excess risk due to vaccine administration usually when only outbreak response were conducted in most part of the year as reflected in the increasing burden of the disease among vaccinated population in 2011, 2013 and 2014. Poor quality outbreak response largely due to improper microplanning, poor cold chain practices and inadequate training are major contributors to ineffectiveness of responses. The overdependence on non-state actors as implementing partners within the context of inadequate legal, regulatory and coordination regime could negatively affect proper supervision and quality assurance monitoring mechanisms for interventions including measles outbreak response. We also noted that the odds of measles in the vaccinated population reduced in a year following the follow-up campaigns as evidenced in 2012 and 2015; however, the level of reduction overlaps with the 95% confidence interval constructs for years where only outbreak response vaccinations were conducted. The follow-up campaigns therefore had higher likelihood of measles risk reduction due to the wider geographic coverage unlike selective vaccination following measles outbreaks.

CONCLUSIONS

Targeted measles outbreak vaccinations generally reduced the burden of measles however the extent of reduction is more reflected in a year following a mass measles campaign as compared to selective vaccination following measles outbreaks. Thus measles follow-up campaigns are necessary for sustained measles control and elimination.

Strengthening routine immunization and case-based surveillance in South Sudan could results in a marked sustainability of achieving measles elimination targets over time; however, due to the current crisis and associated high displaced populations and weakened health infrastructure, follow-up campaigns could make a significant impact on the population in reducing the disease burden towards the global measles elimination goals.

ACKNOWLEDGEMENTS

We thank Boniface Imbani, Melisachew Andane, Taban Musa, Sisto Angelo and Patrick Iranya for the assistance during the investigation.

CONFLICTS OF INTEREST: None.

REFERENCES

1. Perry RT, Halsey NA. The clinical significance of measles: a review. *J Infect Dis*. 2004; 189 Suppl 1: S4-S16. doi: 10.1086/377712

2. Griffin DE, Lin WH, Pan CH. Measles virus, immune control, and persistence. *FEMS Microbiol Rev*. 2012; 36(3): 649-662. doi: 10.1111/j.1574-6976.2012.00330.x

3. World Health Organization. Measles vaccines: WHO position paper. Weekly epidemiological record. 2009; 84(35): 349-360. Web site. http://www.who.int/wer/2009/wer8435.pdf?ua=1. Accessed February 7, 2016.

4. Simons E , Mort M, Dabbagh A, Strebel P, Wolfson L. Strategic planning for measles control: using data to inform optimal vaccination strategies. *J Infect Dis*. 2011; 204Suppl 1: S28-S34. doi: 10.1093/infdis/jir095

5. World Health Organization. *Global measles and rubella, strategic plan: 2012-2020*. Geneva, Switzerland: World Health Organization; 2012: 1-44. Web site. http://apps.who.int/iris/bitstream/10665/44855/1/9789241503396_eng.pdf. Accessed February 7, 2016.

6. who/cds/csr/isr/99.1. *WHO guidelines for epidemic preparedness and response to measles outbreaks*. Geneva, Switzerland: World Health Organization; 1999: 1-51. Web site. http://www.who.int/csr/resources/publications/measles/whocdscsrisr991.pdf. Accessed February 7, 2016.

7. Doshi RH, Shidi C, Mulumba A, et al. The effect of immunization on measles incidence in the Democratic Republic of Congo: Results from a model of surveillance data. *Vaccine*. 2015; 33(48): 6786-6792. doi: 10.1016/j.vaccine.2015.10.020

8. Wang X, Boulton ML, Montgomery JP, et al. The epidemiology of measles in Tianjin, China, 2005-2014. *Vaccine*. 2015; 33(46): 6186-6191. doi: 10.1016/j.vaccine.2015.10.008

9. Verma R, Khanna P, Bairwa M, Chawla S, Prinja S, Rajput M. Introduction of a second dose of measles in national immunization program in India: a major step towards eradication. *Hum Vaccin*. 2011; 7(10): 1109-1011. doi: 10.4161/hv.7.10.16890

10. Nedeljković J, Rakić Adrović S, Tasić G, et al. Resurgence of measles in Serbia 2010-2011 highlights the need for supplementary immunization activities. *Epidemiol Infect*. 2015; 144(5): 1121-1128. doi: 10.1017/S0950268815002277

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-105

11. Scobie HM, Ilunga BK, Mulumba A, et al. Antecedent causes of a measles resurgence in the Democratic Republic of the Congo. *Pan Afr Med J*. 2015; 21: 30. doi: 10.11604/pamj.2015.21.30.6335

12. Babigumira JB, Levin A, Burgess C, et al. Assessing the cost-effectiveness of measles elimination in Uganda: local impact of a global eradication program. *J Infect Dis*. 2011; 204 Suppl 1: S116-S123. doi: 10.1093/infdis/jir132

13. Fowotade A, Okonko IO, Nwabuisi C, Bakare RA, Fadeyi A, Adu FD. Measles vaccine potency and sero-conversion rates among infants receiving measles immunization in Ilorin, Kwara State, Nigeria. *J Immunoassay Immunochem*. 2015; 36(2): 195-209. doi: 10.1080/15321819.2014.920713

14. Simons E, Ferrari M, Fricks J, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. *Lancet*. 2012; 379(9832): 2173-2178. doi: 10.1016/S0140-6736(12)60522-4

15. Nanyunja M, Lewis RF, Makumbi I, et al. Impact of Mass Measles Campaigns among Children Less Than 5 Years Old in Uganda. *J Infect Dis*. 2003; 187 Suppl 1: S63-S68. doi: 10.1086/368026

16. Shibeshi ME, Masresha BG, Smit SB, et al. Measles resurgence in southern Africa: challenges to measles elimination. *Vaccine*. 2014; 32(16): 1798-1807. doi: 10.1016/j.vaccine.2014.01.089

17. Breakwell L, Moturi E, Helgenberger L, et al. Measles Outbreak Associated with Vaccine Failure in Adults — Federated States of Micronesia, February–August 2014. *Morbidity and Mortality Weekly Report (MMWR)-CDC*. 2015; 64(38): 1088-1093. Web site. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6438a7.htm. Accessed February 7, 2016.

18. Levin A, Burgess C, Garrison LP Jr, et al. Global eradication of measles: an epidemiologic and economic evaluation. *J Infect Dis*. 2011; 204 Suppl 1: S98-S106. doi: 10.1093/infdis/jir096

19. Hyde TB, Dayan GH, Langidrik JR, et al. Measles outbreak in the Republic of the Marshall Islands, 2003. *Int J Epidemiol*. 2006; 35: 299-306. doi: 10.1093/ije/dyi222

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

Research

*Corresponding authors

Corresponding author for Germany
Peter Meffert, PhD
Ernst Moritz Arndt University Greifswald
Institute for Community Medicine
Walther-Rathenau-Str. 48
D-17475 Greifswald, Germany
Mob. ++49 15201749393
E-mail: p.j.meffert@web.de

Corresponding author for Chile
Juan F. Miquel, MD
Pontificia Universidad Catolica de Chile
Facultad de Medicina
Departamento de Gastroenterologia
Marcoleta #367, Santiago, Chile
Tel. ++56-2 2639 7780
E-mail: jfmiquel@med.puc.cl

Volume 1 : Issue 1
Article Ref. #: 1000EPOJ1106

Article History
Received: December 31st, 2015
Accepted: April 19th, 2016
Published: April 29th, 2016

Citation
Meffert PJ, Schwittay MA, Lerch MM, et al. Risk factor prevalence and their relative influence on fatty liver and gallstone disease: A cross-ethnic study comparing two high-risk populations from Chile and Northeast Germany. *Epidemiol Open J*. 2016; 1(1): 40-52. doi: 10.17140/EPOJ-1-106

Risk Factor Prevalence and their Relative Influence on Fatty Liver and Gallstone Disease: A Cross-Ethnic Study Comparing Two High-Risk Populations from Chile and Northeast Germany

Peter J. Meffert, PhD[1*]; Maximilian A. Schwittay, MS[1]; Markus M. Lerch, MD, FRCP[2]; Jochen Hampe, MD[3]; Stephan Buch, PhD[3]; Flavio Nervi, MD[4]; Luis Villarroel, PhD[5]; Henry Völzke, MD, PhD[1†]; Juan F. Miquel, MD[4*†]

[†]These authors co-supervised this work and contributed equally

[1]Institute for Community Medicine, Ernst Moritz Arndt University of Greifswald, Greifswald, Germany
[2]Department of Medicine A, Ernst Moritz Arndt University of Greifswald, Greifswald, Germany
[3]1st Medical Department, University Hospital Dresden, Technical University Dresden, Dresden, Germany
[4]Departamento de Gastroenterologia, Facultad de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Chile
[5]División Salud Pública y Medicina Familiar, Facultad de Medicina, Pontificia Universidad Catolica de Chile, Santiago, Chile

ABSTRACT

Objective: Fatty Liver Disease (FLD) and Gallstone disease (GSD) are among the most common gastrointestinal disorders worldwide. Based on data of two ethnically distant populations from Santiago de Chile and Northeast Germany sharing remarkably high prevalence for both diseases, we aimed to estimate (1) the standardised prevalence of FLD and GSD, (2) the population-specific prevalence of known risk factors and (3) the relative influence of each risk factor for the occurrence of the respective outcome.

Design: We used data from two population-based studies from Chile (n=742) and Germany (n=3632). Regression methods were applied to assess the prevalence of risk factors at a specific age. To quantify the relative contribution of the risk factors to the occurrence of FLD and GSD, we used hierarchical variation partitioning.

Results: The standardised prevalence of FLD ranged from 20.7% in Chilean men to 37.9% in German men and the standardised prevalence of GSD from 14.5% in German men to 40.5% in Chilean women. Risk profiles differed considerably between populations and sexes. Overall, the contributions of the risk factors to the occurrence of FLD and GSD coincided widely. For FLD, age and BMI were the predominant factors, followed by serum triglyceride levels and the Single-Nucleotide Polymorphism (SNP) rs738409 C>G of the *PNPLA3* gene. In GSD age was the predominant determinant, in women additionally BMI. Alcohol consumption played a marked role in Chilean men, being positively associated with GSD, similarly the use of contraceptives in Chilean women. The relative contribution of the lithogenic SNP rs11887543 was low in both populations, with marginal effect in Chileans.

Conclusion: Despite marked differences in risk profiles, relative influences of risk factors coincided widely between study populations. Knowledge about importance of risk factors for fatty liver and gallstone disease may guide therapy and advises for lifestyle changes.

KEYWORDS: *PNPLA3*; *ABCG8*; Epidemiology; Hierarchical variation partitioning.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

INTRODUCTION

Gallstone disease (GSD) is one of the most common gastroenterological disorders, affecting 10-20% of the population in Western countries and causing high costs in the health-care systems, e.g. in the USA about 6.5 billion Dollars annually.[1-3] Fatty Liver Disease (FLD) is even more common reaching a prevalence of up to 45% in the general population[4,5] and causing substantial health-care costs.[6] GSD and FLD are showing a rising prevalence since many decades.[7-9]

Both FLD and GSD are multifactorial disorders. In FLD, immutable risk factors are higher age, male sex and genetic risk factors such as the SNP rs738409 (variant p.I148M) of the enzyme adiponutrin (*PNPLA3*).[10] Mutable risk factors include somatometric measurements such as BMI, nutrition, physical activity, alcohol consumption and drugs (e.g. anovulants, fibrates, glucocorticoids) as well as biomarkers such as serum triglyceride levels and diabetes type 2. Non-modifiable risk factors for GSD include advancing age, being female, Amerindian ancestry and carrying common genetic variants such as the SNP rs11887543 (*ABCG8* p.D19H variant).[11] Among the modifiable risk factors are diabetes type 2, obesity, rapid weight loss, diet, hemolysis, drugs and physical activity.[3,12,13] Women are in general of higher risk than men,[14] a phenomenon possibly connected with pregnancy and higher oestrogen levels.[15]

Our study populations were a Hispanic population from the commune La Florida in the Santiago Metropolitan Region in Chile and a Caucasian from Western Pomerania in Northeast Germany. Chileans and Western Pomeranians are among the populations with the highest prevalence of GSD and FLD worldwide.[3,16] The two populations did not differ significantly in the frequency of carrying risk allele for GSD identified so far.[17,18] In this study we aimed to assess standardised prevalence of GSD and FLD, prevalence of risk factors and ascertain the specific contributions of these risk factors in the two populations to the development of FLD and GSD. Consequently, our research questions are: (1) How do prevalence of FLD and GSD differ between the two populations? (2) Are differences in prevalence explained by differences in risk profiles or rather by different susceptibilities for certain risk factors?

METHODS

Populations and Study Designs

The data from the Chilean study population originate from the first follow-up examination of an epidemiological study in an urban area of south Santiago, La Florida, which is representative of the predominant socioeconomic strata and European-Amerindian admixture of the Hispanic Chilean population with 328.881 inhabitants in 1992. Blocks were randomly selected, and then all individuals residing there were enumerated. In the baseline phase, of 2558 selected individuals, 1678 agreed to participate, a response of 65.6%. The current data of 964 subjects aged from 28-89 originate from the first follow-up examination that has been conducted between 2000 and 2001 which corresponds to 57.4% of the initial sample.[16,19] Of these, 63 datasets were incomplete, primarily in genotyping (n=159). Thus, we used 742 complete datasets for the present analyses. For prevalence estimates we used 911 complete datasets.

The German data come from the baseline examination of the Study of Health in Pomerania (SHIP)[20] that includes 4308 subjects. From the total population of Western Pomerania comprising 213,057 inhabitants in 1996, a two-stage stratified random cluster sample of adults aged 20-79 years was drawn. The net sample comprised 6265 eligible subjects. Of these, 4308 subjects (n=2192 women; response of 68.8%) participated in the SHIP baseline examination between 1997 and 2001. In 449 datasets data in the variables of interest were missing, primarily in genotyping (n=252) and alcohol consumption (n=207), thus, the analytic sample comprised of 3632 individuals. For prevalence estimates we used 4124 complete datasets. All patients and controls gave written informed consent prior to the study, and all study protocols have been approved by the Institutional Review and Ethics Committees at the respective sites.

Data Collection and Definitions

The examination protocols included a pre-coded questionnaire on socioeconomic data and medical history, physical and abdominal ultrasonographic examinations (Chile: 3.5-MHz linear transducer, Toosbee, Toshiba, Japan; Germany: 5 MHz transducer and a high-resolution instrument, Vingmed VST Gateway) and biomarker analyses. In both studies, body mass index (BMI) was calculated as kg/m^2. Alcohol consumption was measured as the mean intake of alcohol over the last 30 days, calculated from interview answers. Serum triglycerides and serum glucose were measured with a fasting time of more than eight hours in Chile; in Germany, the median fasting time was 3.5 hours. Diabetes was defined as a pathological serum glucose value of 11.1 mmol/L or higher, antidiabetic medication and/or a self-reported physician's diagnosis. Parity was defined as ever being pregnant or not, also postmenopausal hormone intake and contraceptive intake was defined as 'yes' or 'no'.

FLD was diagnosed after visualisation of a hyperechogenic liver pattern compared to renal parenchyma. Indistinctness of hepatic blood vessels or the diaphragm, decreased acoustic penetration and hepatomegaly were taken into the diagnosis as additional criteria. We did not separate non-alcoholic fatty liver disease (NAFLD) from alcoholic fatty liver disease (AFLD) because we were explicitly interested in the contribution of alcohol consumption to the occurrence of FLD. AFLD and NAFLD share similar histopathological patterns and are only caused by different risk factors.[21] Moreover, the definition of AFLD does depend on the arbitrarily chosen cut-off value for daily alcohol consumption. Based on ultrasound in both studies, GSD was defined as the presence of gallstones or a previous cholecystectomy.[19,20] The SNP rs738409 (common risk variant p.I148M) of the enzyme adiponutrin encoded in the *PNPLA3* gene is a major risk factor for FLD,[22] similarly the SNP rs11887543 (common

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

risk variant p.D19H) of the *ABCG8* gene for GSD.[11] Genotyping of these variants was carried out using the TaqMan SNP genotyping allelic discrimination method (Applied Biosystems, Foster City, CA, USA).

Statistical Analyses

Prevalence data were converted to the world population by direct standardisation by age and sex[23] using the 'dstdize' command in Stata (Stata Corp., College Station, TX, USA). We decided in favour of sex-specific modelling because risk profiles differed substantially between men and women for both phenotypes. Additionally, pathomechanisms are not clear enough to rule out or assume specific sex-specific interactions. Models for FLD were adjusted for age, BMI, alcohol consumption, triglycerides and glucose serum levels, diabetes and SNP rs738409. Models for GSD were adjusted in the same manner but with the SNP rs11887543 and in women additionally for parity, contraceptives and postmenopausal hormones. To quantify the contribution of each risk factor to the phenotypes, we used hierarchical variation partitioning[24] implemented in the package 'hier.part'[25] in the software package R (R Foundation, Vienna, Austria).[26] This method calculates the model fit with all possible combinations of predictor variables and gives the proportion of explained variance for each variable that is explained solely by this variable. We applied the log-likelihood as goodness-of-fit measurement. To account for possible non-linear relations between the predictors and the outcome, we used fractional polynomials.[27] If a two-degree polynomial was fitted for the relationship, we summed up their relative influences resulting from the variation partitioning. To quantify the prevalence of risk factors, we applied median regression for each risk factor and adjusted for age, because median regression does not rely on certain distributional assumptions as e.g. linear (mean) regression. Afterwards, we calculated the respective marginal mean at an age of 50 years to account for changes with age. All models for quantitative outcomes were calculated with robust standard errors.

RESULTS

The analyses included 3632 individuals from Germany (51.1% women) and 742 from Chile (64.6% women). Mean age was 49 years for both samples (standard deviation for Chile: 13 years, SHIP: 16 years).

Prevalence of Fatty Liver Disease, Gallstone Diseases and their Risk Factors

Crude and standardised prevalence data for FLD and GSD are given in Table 1. FLD was much more frequent in German men (37.9%) compared to Chilean men (20.7%). In women, Chileans had a similar prevalence (23.0%) to Germans (21.8%). In contrast, the frequency of GSD was similar between men (Chile: 15.1%, Germany: 14.5%) but differed clearly among women with a much higher proportion in Chileans (40.5%) compared to Germans (26.8%).

Further, we estimated the prevalence of risk factors for FLD and GSD. To enable comparability between the two study groups, we performed median regressions adjusted by age and calculated marginal means at an age of 50 years. Median values of risk factors are given in Table 2. Median alcohol consumption was in general much lower in women than in men and considerably higher in the German compared to the Chilean population. BMI differed significantly only in women with Chilean having a 2.2 kg/m^2 higher BMI than German women. The proportions of diabetes did not differ significantly. Serum triglyceride levels differed only in men and were 0.43 mmol/L (22%) higher in Germans compared to Chileans. Germans had on average higher serum glucose levels than Chileans. The risk G allele frequency of the genetic variant rs738409 at the *PNPLA3* gene was strikingly more frequent in Chile. Similarly but less pronounced the risk C allele frequency of the genetic variant rs11887534 at the *ABCG8* gene was more frequent in the Chilean population. Parity was marginally higher in Chilean women whereas intake of postmenopausal hormones was more frequent in Germany; there was no significant difference in the use of contraceptives.

Relative Influence of Risk Factors on Gallstone Disease and Fatty Liver Disease

We performed regression analyses and then calculated the contribution of each risk factor on the occurrence of FLD and GSD by hierarchical variation partitioning. As a result, this

		Fatty liver disease				Gallstone disease			
Sex/cohort	N	Crude	Standardised	95% CI		Crude	Standardised	95% CI	
Men									
La Florida (Chile)	311	25.7%	20.7%	16.5%	24.9%	14.8%	15.1%	11.1%	19.0%
Northeast Germany	2011	37.3%	37.9%	35.8%	39.9%	14.8%	14.5%	13.0%	15.9%
Women									
La Florida (Chile)	600	24.5%	23.0%	19.6%	26.3%	41.3%	40.5%	36.8%	44.2%
Northeast Germany	2113	21.9%	21.8%	20.2%	23.5%	27.1%	26.8%	25.1%	28.6%

Table 1: Prevalence of fatty liver and gallstone disease for the two cohorts, given is crude and standardised prevalence for the world population.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

	La Florida		Northeast Germany		*p* value	
Risk factor	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Alcohol (g/d)	1.0	0.1	13.4	3.8	$p<0.001$	$p<0.001$
BMI (kg/m²)	27.5	28.8	27.8	26.6	$p=0.313$	$p<0.001$
Diabetes (yes)	9.4%	8.7%	11.1%	6.3%	$p=0.442$	$p=0.063$
Serum triglycerides (mmol/l)	1.50	1.35	1.93	1.34	$p<0.001$	$p=0.698$
Serum glucose (mmol/l)	5.06	4.95	5.45	5.22	$p<0.001$	$p<0.001$
SNP rs738409 (number of G allele copies)	1.03	1.10	0.44	0.47	$p<0.001$	$p<0.001$
SNP rs11887534 (number of C allele copies)	0.16	0.19	0.11	0.12	$p=0.047$	$p<.001$
Parity	–	96.8%	–	94.5%	$p=0.017$	
Postmenopausal hormones	–	11.5%	–	24.0%	$p<0.001$	
Contraceptives	–	50.6%	–	51.5%	$p=0.812$	

Table 2: Frequencies of risk factors for gallstone disease and fatty liver disease in La Florida (Chile) and Northeast Germany; values are margins at an age of 50 years (except SNP rs738409 and rs11887543; contraceptives are given for an age of 25 years) of median regressions for continuous outcomes (given are medians), logistic regression for binary outcomes (given are probabilities) and Poisson regression for number of G allele copies of rs738409 and rs11887534, respectively.

method gives the independent influence of each variable.

Logistic regression models for the occurrence of FLD and GSD comprised age, BMI, alcohol consumption, serum triglycerides, serum glucose, and diabetes type 2, in FLD additionally the SNP rs738409 and in GSD additionally the SNP rs11887534 as well as parity, contraceptives and postmenopausal hormones in women. For non-linear associations, dependent variables were transformed using fractional polynomials.[27] The regression tables are given in the Appendix.

The regression models for FLD had AUC (area under the Receiver-Operation-Characteristic curve) values ranging from 0.79 to 0.88 (Chilean men: AUC=0.841, women: AUC=0.829; German men: AUC=0.794, women: AUC=0.884; ROC curves are given as supplementary data in the Appendices (A 9-A 16); pseudo-R^2 values varied between 0.21 and 0.36 (Chilean men: pseudo R^2=0.260, women: pseudo R^2=0.239; German men: pseudo R^2=0.211, women: pseudo R^2=0.356). In Chilean men, occurrence of FLD was mainly influenced by the risk factors BMI and serum triglycerides, followed by the SNP rs738409; age, alcohol consumption, serum glucose level and diabetes status were of less importance; in German men, also BMI and serum triglycerides were important, additionally age (Figure 1A). The influence of alcohol consumption and serum glucose levels were weak in both cohorts but stronger in Germans compared to Chileans. The SNP rs738409 was of similar influence as in Chilean and German men. German women did not considerably differ from German man in the relative contribution of risk factors (Figure 1). However, in Chilean women there was a shift: compared to all other groups, serum triglyceride levels were less important, whereas the SNP rs738409 was much more influential having more than 30% relative influence on the occurrence of FLD (Figure 1 B). It is also striking that age provides a major influence in Germans but is neglectable in Chileans of both sex. The immutable risk factors age and rs738409 contributed together with 11.9% in Chilean men, 39.3% in German men, 31.1% in Chilean women and 28.8% in German women.

In GSD models, AUC ranged from 0.74 to 0.79 (Chilean men: AUC=0.742, women: AUC=0.741; German men: AUC=0.772, women: AUC=0.789), pseudo-R^2 values were lower compared to FLD models (Chilean men: pseudo R^2=0.102, women: pseudo R^2=0.133; German men: pseudo R^2=0.148, women: pseudo R^2=0.190). In German men only age and BMI had a relative influence above 10%, whereas in Chilean men age and alcohol consumption contributed considerably to the occurrence of GSD (Figure 2A). Serum triglycerides, serum glucose and diabetes played only a marginal role, in Chile BMI was also not an important factor. While in German men alcohol was non-significant inversely related to GSD (OR=0.993, 95% CI: 0.983-1.002, p=0.119, Table A 6 of the Appendix), it was positively associated with GSD in Chilean men (OR=1.017, 95% CI: 0.999-1.036, p=0.066; Table A 5 of the Appendix) being borderline statistical significant. In women both age and BMI contributed substantially to the occurrence of GSD, in Chileans additionally use of contraceptives (Figure 2 B). In German women, the C allele of the SNP rs11887534 contributed with 10%, in the other groups between 0% and 5% with a stronger influence in Germans. The influence of the other risk factors ranged between 0% and 7%. The contribution of immutable risk factors age and SNP rs11887534 was low (7.2% in Chilean men, 1.9% in German men, 3.0% in Chilean women and 5.9% in German women).

DISCUSSION

We compared the prevalence of FLD and GSD between two ethnically different populations from Chile and Germany. Additionally, we assessed the occurrence of known risk factors for both disorders. Finally, we calculated the relative contribution of each risk factor to the occurrence of FLD and GSD.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

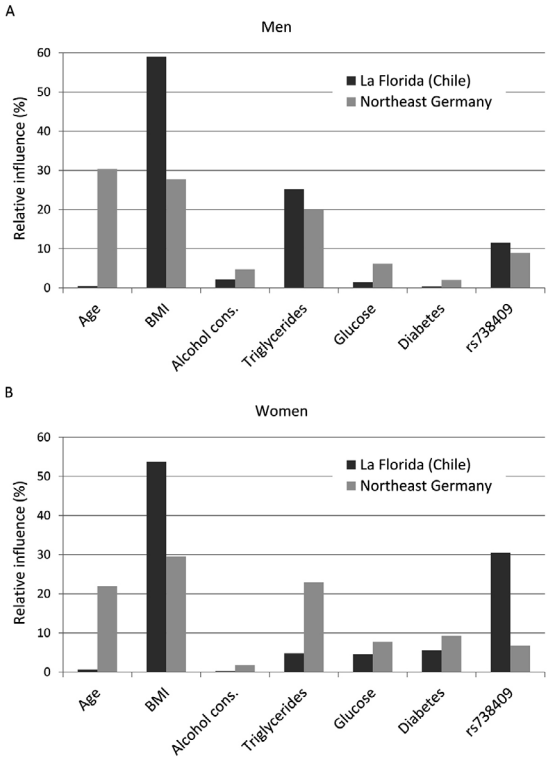


Figure 1: Relative independent influences of risk factors on the occurrence of fatty liver disease for men (A) and women (B); cons.: consumption; Postm.: postmenopausal; horm.: hormones.

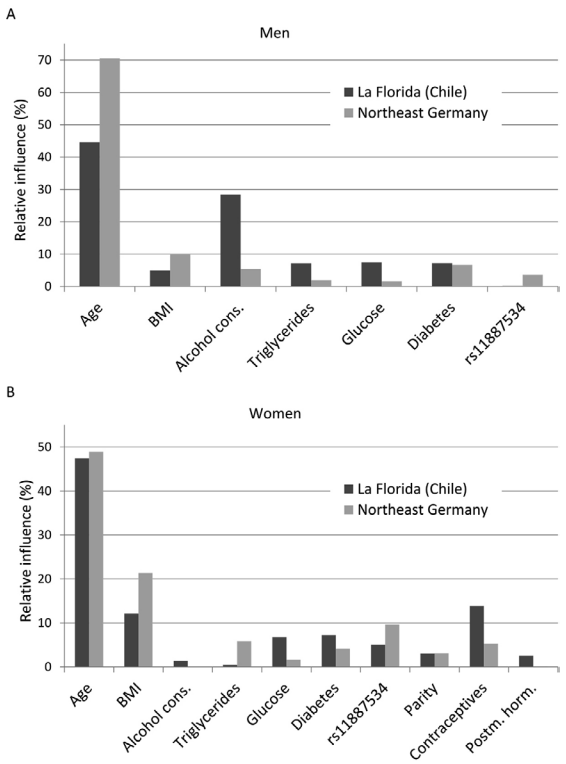


Figure 2: Relative independent influences of risk factors on the occurrence of gallstone disease for men (A) and women (B); cons.: consumption; Postm.: postmenopausal; horm.: hormones.

Fatty Liver Disease

In our populations, FLD had a standardised prevalence of 20.8% to 23.1% with the exception of men from the SHIP that showed even a 37.5% prevalence (Table 1). Standardisation to the world population decreased the prevalence in Chile by five percent points. Worldwide prevalence of NAFLD, which make up the vast majority of FLD, has an assumed median of 20%.[28] Population-based data from South America are scarce[29]; in Mexico the prevalence of NAFDL was 17.1%,[30] and 23% in the same Chilean population we analysed for the current analysis.[31] Regarding the exclusion of individuals with high levels of alcohol consumption for NAFDL in these reports, this might be of about the same prevalence as our findings. Two southwest German cohorts showed a lower prevalence of 24.0% and 18.7% (men and women combined) compared to our data.[32] In the United States, the prevalence were of similar magnitude as in Western Pomerania: the Dallas Heart Study found 33.6% FLD measured by 1H magnetic resonance spectrography,[33] in another population-based study the prevalence of NAFLD was 21.4%.[34] The estimated prevalence highly depends on diagnostic tools (ultrasound, tomography, enzymes, biopsy, autopsy), on age and sex distributions and study design.[28] The high prevalence in German men is plausible in the light of the high alcohol consumption, the high prevalence of diabetes and the high serum triglyceride levels (Table 2).

The relative contribution of each risk factor to the occurrence of FLD varied between the Chilean and the German population as well as between men and women. The most obvious difference between the study populations was the influence of age and BMI. This could possibly be attributed to the fact that elder Germans were on average more obese than younger ones, whereas elder Chileans have on average a lower BMI compared to middle-aged subjects. Here, the cross-sectional nature of the data has to be kept in mind: possibly, a change in lifestyle had occurred only in younger Chileans but not in elder ones. In consequence, age and BMI should have to be considered together rather than as single factors. In fact, the sum of the relative influences of age and BMI is comparable for Chile and the SHIP. Alternatively, Chileans may develop FLD and obesity earlier in life compared to Germans or independent of age because of life styles or genetic factors such as rs738409 or others to be discovered.

The SNP rs738409 had an influence of about 10% in SHIP and Chilean men despite the prevalence of the risk G allele was more than 130% higher in the Chilean compared to the German population in men and women. However, a major finding of this cross-ethnic study is that in Chilean women the relative contribution of the PNPL3 risk variant was above 30%. Inversely, serum triglycerides accounted for about 20% of the variation of FLD in men and women from the SHIP but only for 5% in Chilean women. Possibly, *PNPLA3* gene is very closely connected with triglyceride storage and might be an explanation for the low impact of serum triglycerides in Chilean women. For the Chilean data but not for the German data, we also confirm previous findings[10] that the influence of the SNP rs738409 on liver fat content is stronger in women than in men. An association of the rs738409 G allele with lower fasting serum triglycerides in

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

overweight and obese individuals was found in two genetic studies[35,36] and a cohort in northern Europe.[37] Conceivably, the G allele of the rs738409 variant could cause an impaired hepatic triglycerides efflux resulting in lower serum triglycerides *via* a reduction of the very low density lipoprotein (VLDL) lipidation.[37] Finally, the risk G allele of the *PNPLA3* gene has been reported not only to be strongly associated with altered lipometabolism, but with chronic liver disease severity and progression.[37,38] Since heritability of NAFLD has been estimated to be as high as 50% in some populations,[39] this single *PNPLA3* risk variant may explain about 60% of the heritability of fatty liver disease in Chilean women. Thus, at least in Chilean women, the evaluation of this risk variant may be a cornerstone in implementation of early detection and preventive actions for chronic liver diseases.

The influences of alcohol consumption, serum glucose and diabetes on FLD were low in both populations and sexes.

Gallstone Disease

The standardised prevalence of GSD in Chile was 15.1% for men and 40.5% for women, very similar to the original data reported for the entire cohort[16] and one of the highest prevalence reported worldwide. The mean prevalence of GSD in European populations is 10-12%,[40] a large study from Italy shows a prevalence of 8.5% for men and 18.9% for women.[41] As reported earlier,[3] Northeast Germany is a high-prevalence area for GSD. In contrast, two studies from Denmark report a much lower prevalence (men: 5.7%, women: 11.9%[42] and men: 6.0%, women: 13.1%,[43] respectively). Possibly, these dissimilarities are caused by considerable differences in BMI between Denmark and Germany. However, in the last-mentioned study, differences between known risk factors were only partly able to explain the difference in GSD prevalence between Denmark and Northeast Germany.

In GSD, age was the superior explanation in all groups, consistent with the chronic nature of this metabolic disease. In men, only alcohol consumption in Chileans had additionally a considerable relative influence with higher alcohol consumption being associated with a higher risk of GSD. Since German men drank much more alcohol, our data suggest that the amount of alcohol consumption is in Chileans more closely related to the occurrence of GSD. This could be attributed to genetic differences that cause differences in metabolism. A case-control study from Australia reported a protective effect of alcohol,[44] but confounding cannot be ruled out for this finding. In women, the differences in the relative influence of BMI was higher for Chileans compared to Germans (22% *versus* 12%, respectively) and this trend is also observed in men, but the relative influence was lower. The differences in the relative contribution of serum triglycerides, serum glucose and diabetes were in general small.

Although the prevalence of risk factors for GSD differed substantially between German and Chilean women, their relative influences were comparable. Thus, what caused the extraordinary high prevalence in Chilean Women? Indeed, Chilean women had higher BMI, serum glucose levels and were more often pregnant than German women, but they also used less contraceptives and postmenopausal hormones. We assume that beyond BMI, an unmeasured factor contributed to the high prevalence in Chilean women. Model performances for GSD were worse for the Chilean data than for the German data, with smaller AUC and pseudo-R^2 values. This could be indicative of one or several risk factors that occur only in the Chilean population. One possibility are specific not yet discover lithogenic genes, most probably associated to their Amerindian admixture.[16,45] Indeed, we and others have proposed that heritability of GSD is significantly higher in Native Americans and admixture populations with Amerindian ancestry compared to other populations.[46] The SNP rs11887534 indeed did explain some variation in GSD and had an odds ratio of about two in the German population, but it was able to explain only a comparatively small proportion of variance in the data. It is noteworthy that, although the frequency of this risk allele is significantly higher in Chileans, its effect on GSD risk was very small in Chileans compared to Germans. Possibly, other yet undiscovered genetic variants as well as gene-gene and gene-environment interactions may act beyond the impact of the single SNP, especially in Hispanics. BMI and serum triglycerides were slightly more important in the SHIP, whereas contraceptives had a stronger influence in Chile. Contraceptives may differ in their impact on GSD,[47,48] and possibly, compounds used in Chile differ from those used in Germany; unfortunately data on the specific compounds were not available in our study. Moreover, the impact of contraceptives might be modified by different levels of BMI.[49] The relative influence of BMI on GSD was in both populations much higher in women than in men. This corresponds to previous findings where obesity was associated with an increased risk of GSD in young women only.[44]

STRENGTHS AND LIMITATIONS

The strength of our data is the population-based design for both cohorts and a comparable data acquisition in a relatively short period in between 1997 to 2001. Limiting factors are that we do not have comparable data on socioeconomic status, diet, family history and physical activity and are thus not able to address the influences of these factors.

CONCLUSIONS

Overall, the contributions of the risk factors to the occurrence of FLD and GSD coincided widely, but not for all variables. A particularly strong influence on the occurrence of FLD had age in Germans and BMI in Chileans, further the SNP rs738409 in Chilean women, whereas the influence of serum triglycerides was exceptionally weak in this group. For GSD, particularly strong influence had alcohol consumption in Chilean men and use of contraceptives in Chilean women.

ACKNOWLEDGEMENTS

The SHIP is part of the Community Medicine Research net of

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants no. 01ZZ9603, 01ZZ0103, 01ZZ0403 and 03IS2061A), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania. The Chilean study has been supported by Fondo Nacional Científico y Tecnológico (FONDECYT, grant no. 1130303 to JFM and and no. 1100020 to FN) and the FONDAP Center for Genome Regulation (grant no. 15090007) to JFM. The authors thank the community of La Florida, without whose participation and encouragement these studies could not have been performed.

CONFLICTS OF INTEREST: None.

REFERENCES

1. Shaffer EA. Gallstone disease: Epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol.* 2006; 20(6): 981-996. doi: 10.1016/j.bpg.2006.05.004

2. Lammert F, Sauerbruch T. Mechanisms of disease: the genetic epidemiology of gallbladder stones. *Nat Clin Pract Gastroenterol Hepatol.* 2005; 2(9): 423-433. doi: 10.1038/ncpgasthep0257

3. Völzke H, Baumeister SE, Alte D, et al. Independent risk factors for gallstone formation in a region with high cholelithiasis prevalence. *Digestion.* 2005; 71(2): 97-105. doi: 10.1159/000084525

4. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology.* 2004; 40(6): 1387-1395. doi: 10.1002/hep.20466

5. Meffert PJ, Baumeister SE, Lerch MM, Mayerle J, Kratzer W, Volzke H. Development, external validation, and comparative assessment of a new diagnostic score for hepatic steatosis. *Am J Gastroenterol.* 2014; 24(10): 1404-1414. doi: 10.1038/ajg.2014.155

6. Baumeister SE, Völzke H, Marschall P, et al. Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. *Gastroenterology.* 2008; 134(1): 85-94. doi: 10.1053/j.gastro.2007.10.024

7. Plant JC, Percy I, Bates T, Gastard J, de Nercy YH. Incidence of gallbladder disease in Canada, England, and France. *Lancet.* 1973; 2(7823): 249-251. doi: 10.1016/S0140-6736(73)93148-6

8. Bateson MC. Gallstones and cholecystectomy in modern Britain. *Postgrad Med J.* 2000; 76(901): 700-703. doi: 10.1136/pmj.76.901.700

9. Welsh JA, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. *J Pediatr.* 2013; 162(3): 496-500. doi: 10.1016/j.jpeds.2012.08.043

10. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology.* 2011; 53(6): 1883-1894. doi: 10.1002/hep.24283

11. von Kampen O, Buch S, Nothnagel M, et al. Genetic and functional identification of the likely causative variant for cholesterol gallstone disease at the ABCG5/8 lithogenic locus. *Hepatology.* 2013; 57(6): 2407-2417. doi: 10.1002/hep.26009

12. Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? *Curr Gastroenterol Rep.* 2005; 7(2): 132-140. doi: 10.1007/s11894-005-0051-8

13. Shaffer EA. Epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol.* 2006; 20(6): 981-996. doi: 10.1016/j.bpg.2006.05.004

14. Aerts R, Penninckx F. The burden of gallstone disease in Europe. *Aliment Pharmacol Ther.* 2003; 3: 49-53. doi: 10.1046/j.0953-0673.2003.01721.x

15. Jorgensen T. Gall stones in a Danish population: fertility period, pregnancies, and exogenous female sex hormones. *Gut.* 1988; 29(4): 433-439. doi: 10.1136/gut.29.4.433

16. Miquel JF, Covarrubias C, Villaroel L, et al. Genetic epidemiology of cholesterol cholelithiasis among Chilean Hispanics, Amerindians, and Maoris. *Gastroenterology.* 1998; 115(4): 937-946.

17. Buch S, Schafmayer C, Völzke H, et al. Loci from a genome-wide analysis of bilirubin levels are associated with gallstone risk and composition. *Gastroenterology.* 2010; 139(6): 1942-1951. doi: 10.1053/j.gastro.2010.09.003

18. Buch S, Schafmayer C, Völzke H, et al. A genome-wide association scan identifies the hepatic cholesterol transporter ABCG8 as a susceptibility factor for human gallstone disease. *Nat Genet.* 2007; 39(8): 995-999. doi: 10.1038/ng2101

19. Nervi F, Miquel JF, Alvarez M, et al. Gallbladder disease is associated with insulin resistance in a high risk Hispanic population. *J Hepatol.* 2006; 45(2): 299-305. doi: 10.1016/j.jhep.2006.01.026

20. Völzke H, Alte D, Schmidt CO, et al. Cohort profile: The study of health in pomerania. *Int J Epidemiol.* 2011; 40(2): 294-307. doi: 10.1093/ije/dyp394

21. Völzke H. Multicausality in fatty liver disease: Is there a rationale to distinguish between alcoholic and non-alcoholic origin? *World J Gastroenterol.* 2012; 18(27): 3492-3501. doi: 10.3748/wjg.v18.i27.3492

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

22. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet.* 2008; 40(12): 1461-1465. doi: 10.1038/ng.257

23. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. GPE Discussion Paper Series: World Health Organization, 2001. Web site. http://www.who.int/healthinfo/paper31.pdf. Accessed December 30, 2015.

24. Chevan A, Sutherland M. Hierarchical partitioning. *Am Stat.* 1991; 45(2): 90-96. doi: 10.2307/2684366

25. Walsh C, MacNally R. Hierarchical partitioning. *The R Project for Statistical Computing.* 2004.

26. R Development Core Team. R: A language and environment for statistical computing. *R Foundation for Statistical Computing Vienna Austria* 2010.

27. Sauerbrei W, Royston P. Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. *J R Stat Soc: Series A.* 1999; 162(1): 71-94. doi: 10.1111/1467-985X.00122

28. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther.* 2011; 34(3): 274-285. doi: 10.1111/j.1365-2036.2011.04724.x

29. Lopez-Velazquez JA, Silva-Vidal KV, Ponciano-Rodriguez G, et al. The prevalence of nonalcoholic fatty liver disease in the Americas. *Ann Hepatol.* 2014; 13(2): 166-178. Web site. http://www.annalsofhepatology.com/revista/numeros/2014/03_142_v13n2_2014_PrevalenceNonalcoholic.pdf. Accessed December 30, 2015.

30. Lizardi-Cervera J, Laparra D, Chavez-Tapia N, Ostos M, Esquivel M. Prevalence of NAFLD and metabolic syndrome in asymptomatic subjects. *Rev Gastroenterol Mex.* 2006; 71: 453-459.

31. Riquelme A, Arrese M, Soza A, et al. Non-alcoholic fatty liver disease and its association with obesity, insulin resistance and increased serum levels of C-reactive protein in Hispanics. *Liver Int.* 2009; 29(1): 82-88. doi: 10.1111/j.1478-3231.2008.01823.x

32. Boehm BO, Claudi-Boehm S, Yildirim S, et al. Prevalence of the metabolic syndrome in southwest Germany. *Scand J Clin Lab Invest Suppl.* 2005; 240: 122-128.

33. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol-endoc M.* 2005; 288(2): E462-E468. doi: 10.1152/ajpendo.00064.2004

34. Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of Nonalcoholic Fatty Liver Disease in the United States: The Third National Health and Nutrition Examination Survey, 1988-1994. *Am Journal Epidemiol.* 2013; 178(1): 38-45. doi: 10.1093/aje/kws448

35. Kollerits B, Coassin S, Beckmann ND, et al. Genetic evidence for a role of adiponutrin in the metabolism of apolipoprotein B-containing lipoproteins. *Hum Mol Genet.* 2009; 18(23): 4669-4676. doi: 10.1093/hmg/ddp424

36. Krawczyk M, Gruenhage F, Mahler M, Tirziu S, Acalovschi M, Lammert F. The common adiponutrin variant p.I148M does not confer gallstone risk but affects fasting glucose and triglyceride levels. *J Physiol Pharmacol.* 2011; 62(3): 369-375. Web site. http://www.jpp.krakow.pl/journal/archive/06_11/pdf/369_06_11_article.pdf. Accessed December 30, 2015.

37. Palmer CN, Maglio C, Pirazzi C, et al. Paradoxical lower serum triglyceride levels and higher type 2 diabetes mellitus susceptibility in obese individuals with the PNPLA3 148M variant. *PLoS One.* 2012; 7(6): e39362. doi: 10.1371/journal.pone.0039362

38. Krawczyk M, Portincasa P, Lammert F. PNPLA3-associated steatohepatitis: toward a gene-based classification of fatty liver disease. *Semin Liver Dis.* 2013; 33(4): 369-379. doi: 10.1055/s-0033-1358525

39. Schwimmer JB, Celedon MA, Lavine JE, et al. Heritability of nonalcoholic fatty liver disease. *Gastroenterology.* 2009; 136(5): 1585-1592. doi: 10.1053/j.gastro.2009.01.050

40. Kratzer W, Mason RA, Kachele V. Prevalence of gallstones in sonographic surveys worldwide. *J Clin Ultrasound.* 1999; 27(1): 1-7. doi: 10.1002/(SICI)1097-0096(199901)27:1<1::AID-JCU1>3.0.CO;2-H

41. Attili AF, Carulli N, Roda E, et al. Epidemiology of gallstone disease in Italy: prevalence data of the Multicenter Italian Study on Cholelithiasis (M.I.COL.). *Am J Epidemiol.* 1995; 141(2): 158-165.

42. Jorgensen T. Prevalence of gallstones in a Danish population. *Am J Epidemiol.* 1987; 126(5): 912-921.

43. Friedrich N, Völzke H, Hampe J, Lerch MM, Jorgensen T. Known risk factors do not explain disparities in gallstone prevalence between denmark and northeast Germany. *Am J Gastroenterol.* 2009; 104(1): 89-95. doi: 10.1038/ajg.2008.13

44. Scragg RK, McMichael AJ, Baghurst PA. Diet, alcohol, and relative weight in gall stone disease: a case-control study. *Br Med J.* 1984; 288(6424): 1113-1119.

45. Nervi F, Miquel JF, Marshall G. The Amerindian epidemics of cholesterol gallstones: the North and South connection. *Hep-*

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

atology. 2003; 37(4): 947-948. doi: 10.1053/jhep.2003.50140

46. Krawczyk M, Miquel JF, Stokes CS, et al. Genetics of biliary lithiasis from an ethnic perspective. *Clin Res Hepatol Gastroenterol.* 2013; 37(2): 119-125. doi: 10.1016/j.clinre.2012.09.002

47. Thijs C, Knipschild P. Oral contraceptives and the risk of gallbladder disease: a meta-analysis. *Am J Public Health.* 1993; 83(8): 1113-1120.

48. Etminan M, Delaney JA, Bressler B, Brophy JM. Oral contraceptives and the risk of gallbladder disease: a comparative safety study. *CMAJ.* 2011; 183(8): 899-904. doi: 10.1503/cmaj.110161

49. Wang FZ, Shen XF, Guo XR, Peng YZ. Oral contraceptives and risk of gallbladder disease. *CMAJ.* 2011; 183(13): 1517. doi: 10.1503/cmaj.111-2065

EPIDEMIOLOGY

Openventio PUBLISHERS

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

APPENDIX

	Odds Ratio	*p* value	95% CI	
Age (years)	0.986	0.352	0.958	1.015
BMI polynomial 1[1] (kg/m²)	2.981	<0.001[5]	1.506	5.901
BMI polynomial 2[2] (kg/m²)	0.507		0.324	0.794
Alcohol (g/d)	1.014	0.127	0.996	1.033
Serum triglycerides polynomial 1[3] (mmol/l)	1.2E-04	0.014[5]	7.5E-10	20.00
Serum triglycerides polynomial 2[4] (mmol/l)	1.1E-16		5.7E-29	2.1E-04
Serum glucose (mmol/l)	0.832	0.252	0.607	1.140
Diabetes (yes)	1.037	0.963	0.224	4.795
SNP rs738409	1.799	0.014	1.125	2.876

[1]transformation: $(BMI/10)^3$
[2]transformation: $(BMI/10)^3 * \ln(BMI/10)$
[3]transformation: $(triglycerides/10)^3$ (mmol/l)
[4]transformation: $(triglycerides/10)^3 * \ln(triglycerides/10)$ (mmol/l)
[5]joint test for both variables

A 1: Regression table for fatty liver disease in Chilean men.

	Odds Ratio	*p* value	95% CI	
Age polynomial 1[1] (years)	204.0	<0.001[3]	42.8	971.6
Age polynomial 2[2] (years)	0.910		0.880	0.940
BMI (kg/m²)	1.178	<0.001	1.139	1.218
Alcohol (g/d)	1.014	<0.001	1.007	1.020
Serum triglycerides (mmol/l)	1.431	<0.001	1.304	1.571
Serum glucose (mmol/l)	1.154	0.002	1.055	1.262
Diabetes (yes)	1.072	0.726	0.727	1.581
SNP rs738409	1.521	<0.001	1.251	1.849

[1]transformation: $(age/10)^{0.5}$
[2]transformation: $(age/10)^2$
[3]joint test for both variables

A 2: Regression table for fatty liver disease in men from the SHIP.

	Odds Ratio	*p* value	95% CI	
Age (years)	0.992	0.419	0.973	1.012
BMI polynomial[1] (kg/m²)	2.9E-13	<0.001	7.0E-17	1.2E-09
Alcohol (g/d)	0.973	0.583	0.883	1.073
Serum triglycerides (mmol/l)	1.438	0.014	1.076	1.921
Serum glucose (mmol/l)	1.095	0.178	0.959	1.250
Diabetes (yes)	2.891	0.065	0.936	8.926
SNP rs738409	1.813	0.001	1.276	2.577

[1]transformation: $(BMI/10)^{-2}$

A 3: Regression table for fatty liver disease in Chilean women.

ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

	Odds Ratio	*p* value	95% CI	
Age polynomial[1] (years)	6.3E-09	<0.001	2.4E-11	1.7E-06
BMI (kg/m^2)	1.157	<0.001	1.123	1.192
Alcohol polynomial 1[2] (g/day)	1.191	<0.001[4]	1.086	1.306
Alcohol polynomial 2[3] (g/day)	1.015		1.007	1.022
Serum triglycerides (mmol/l)	2.128	<0.001	1.829	2.477
Serum glucose (mmol/l)	1.175	0.013	1.035	1.333
Diabetes (yes)	2.559	<0.001	1.517	4.316
SNP rs738409	1.866	<0.001	1.490	2.339

[1]transformation: (age/10)$^{-2}$
[2]transformation: ((alcohol)/100)$^{-0.5}$
[3]transformation: ((alcohol)/100)$^{-0.5}$ * ln((alcohol)/100)
[4]joint test for both variables

A 4: Regression table for fatty liver disease in women from the SHIP.

	Odds Ratio	*p* value	95% CI	
Age (years)	1.052	0.004	1.017	1.090
BMI (kg/m^2)	1.041	0.318	0.962	1.126
Alcohol (g/d)	1.017	0.066	0.999	1.036
Triglycerides (mmol/l)	1.211	0.198	0.904	1.623
Glucose (mmol/l)	0.718	0.061	0.508	1.016
Diabetes (yes)	2.659	0.265	0.476	14.862
SNP rs11887534	1.174	0.751	0.434	3.174

A 5: Regression table for gallstone disease in Chilean men.

	Odds Ratio	*p* value	95% CI	
Age (years)	1.062	<0.001	1.051	1.073
BMI (kg/m^2)	1.078	<0.001	1.036	1.122
Alcohol (g/d)	0.993	0.119	0.983	1.002
Triglycerides (mmol/l)	1.080	0.070	0.994	1.173
Glucose polynomial[1] (mmol/l)	1.148	0.053	0.998	1.319
Diabetes (yes)	1.532	0.036	1.029	2.281
SNP rs11887534	1.926	0.001	1.319	2.813

[1]transformation: (glucose/10)$^{-2}$

A 6: Regression table for gallstone disease in men from the SHIP.

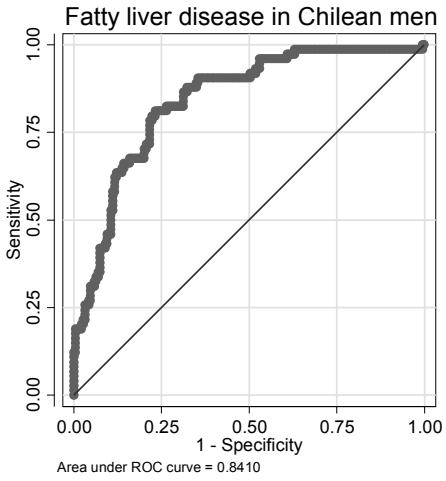
	Odds Ratio	*p* value	95% CI	
Age (years)	1.046	<0.001	1.027	1.065
BMI (kg/m^2)	1.059	0.007	1.015	1.104
Alcohol (g/d)	1.032	0.206	0.983	1.083
Triglycerides (mmol/l)	0.964	0.776	0.752	1.237
Glucose (mmol/l)	1.049	0.468	0.922	1.193
Diabetes (yes)	1.485	0.444	0.539	4.093
Parity (yes)	2.572	0.121	0.778	8.497
Contraceptives (yes)	0.476	0.039	0.235	0.962
Postmenopausal hormones (yes)	1.562	0.177	0.818	2.985
SNP rs11887534	1.456	0.125	0.901	2.352

A 7: Regression table for gallstone disease in Chilean women.

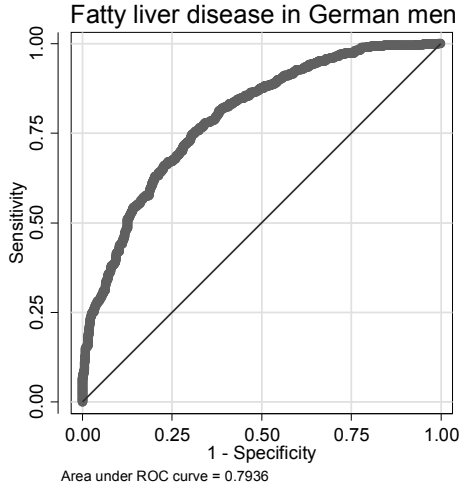
ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106

	Odds Ratio	*p* value	95% CI	
Age (years)	1.058	<0.001	1.048	1.068
BMI (kg/m²)	1.085	<0.001	1.060	1.110
Alcohol (g/d)	1.001	0.905	0.985	1.017
Triglycerides (mmol/l)	1.140	0.010	1.032	1.260
Glucose (mmol/l)	0.931	0.130	0.849	1.021
Diabetes (yes)	1.350	0.172	0.878	2.075
Parity (yes)	1.665	0.022	1.075	2.577
Contraceptives (yes)	1.157	0.497	0.760	1.760
Postmenopausal hormones (yes)	0.971	0.826	0.745	1.265
SNP rs11887534	2.150	<0.001	1.590	2.906

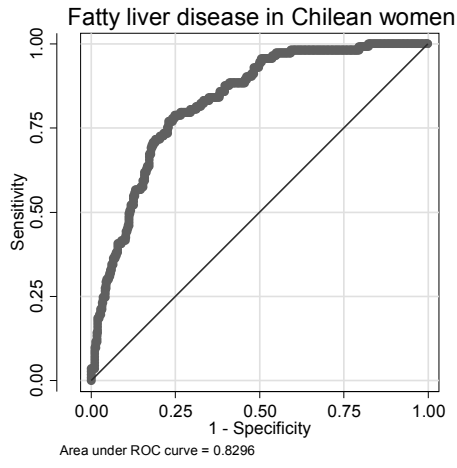
A 8: Regression table for gallstone disease in women from the SHIP.



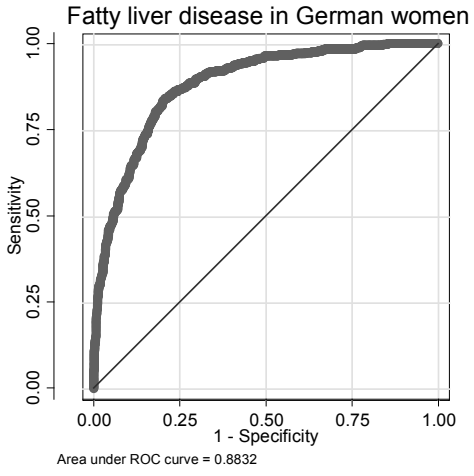
A 9: ROC curve for fatty liver disease in Chilean men.



A 10: ROC curve for fatty liver disease in German men.

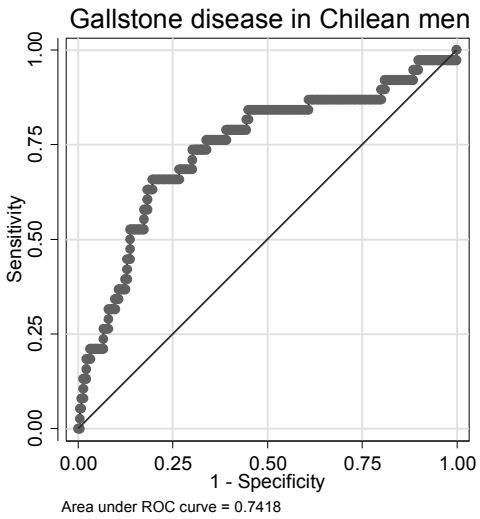


A 11: ROC curve for fatty liver disease in Chilean women.

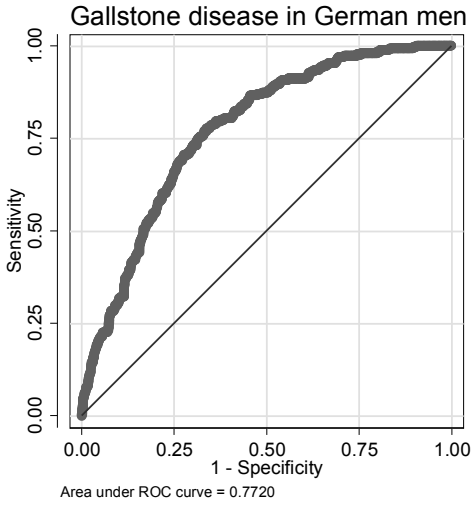


A 12: ROC curve for fatty liver disease in German women.

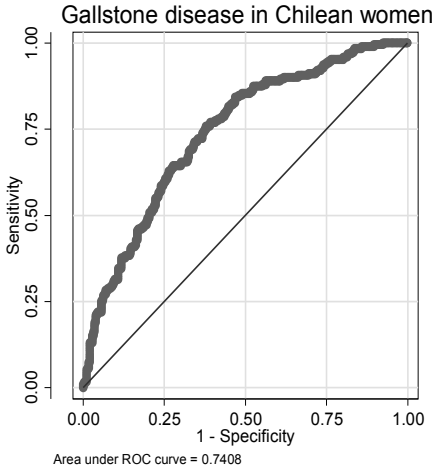
ISSN 2473-4780 Open Journal http://dx.doi.org/10.17140/EPOJ-1-106



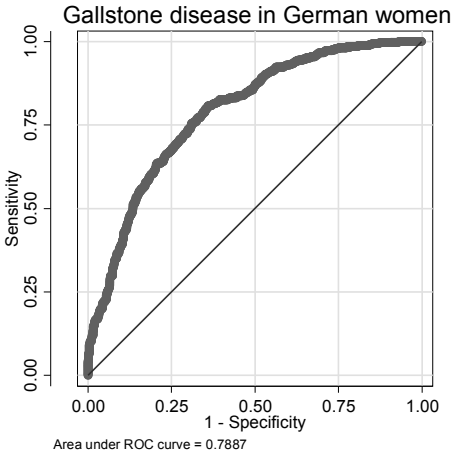
A 13: ROC curve for gallstone disease in Chilean men.



A 14: ROC curve for gallstone disease in German men.



A 15: ROC curve for gallstone disease in Chilean women.



A 16: ROC curve for gallstone disease in German women.