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Model-based recursive partitioning to identify risk clusters for metabolic syndrome and its components: Findings from the International Mobility in Aging Study

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Title: Model-based recursive partitioning to identify risk clusters for metabolic syndrome and its components: Findings from the International Mobility in Aging Study

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ABSTRACT

Objective: Conceptual models underpinning much epidemiological research on aging acknowledge that environmental, social, and biological systems *interact* to influence health outcomes. Recursive partitioning is a data-driven approach that allows for concurrent exploration of distinct mixtures, or clusters, of individuals that have a particular outcome. Our aim is to use recursive partitioning to examine risk clusters for metabolic syndrome (MetS) and its components, in order to identify vulnerable populations.

Study Design: Cross-sectional analysis of baseline data from a prospective longitudinal cohort called the International Mobility in Aging Study (IMIAS).

Setting: IMIAS includes sites from three middle-income countries- Tirana (Albania), Natal (Brazil), and Manizales (Colombia)- and two from Canada- Kingston (Ontario) and Saint-Hyacinthe (Quebec).

Participants: Community-dwelling male and female adults, ages 64 to 75 (N=2002).

Primary and Secondary Outcome Measures: We apply recursive partitioning to investigate social and behavioural risk factors for MetS and its components. Model-based recursive partitioning (MOB) was used to cluster participants into age-adjusted risk groups based on variabilities in: study site, sex, education, living arrangements, childhood adversities, adult occupation, current employment status, income, perceived income sufficiency, smoking status, and weekly minutes of physical activity.

Results: 43% of participants had MetS. Using MOB, the primary partitioning variable was participant sex. Among women from middle-incomes sites, the predicted proportion with MetS ranged from 58 to 68%. Canadian women with limited physical activity had elevated predicted proportions of MetS (49%, 95%CI 39-58%). Among men, MetS ranged from 26% to 41% depending on childhood social adversity and education. Clustering for MetS components differed from the syndrome and across components. Study site was a primary partitioning variable for all components except HDL cholesterol. Sex was important for most components.

Conclusion: MOB is a promising technique for identifying disease risk clusters (e.g. vulnerable populations) in modestly sized samples.

Key words: Recursive partitioning; Metabolic syndrome; Older adults; Global health

ARTICLE SUMMARY

Strengths and limitations of this study

- Explores social and behavioural risk clustering for metabolic syndrome among community-dwelling older adults from five diverse global settings
- Applies model-based recursive partitioning, which is more intuitive and computationally efficient than Classification and Regression Trees (CART), to identify risk clusters
- Provides an example of how model-based recursive partitioning can be used in a modestly-sized sample for hypothesis generation about complex admixtures of risk factors
- Lacks data on participant diet, which likely clusters with many of the social and behavioural factors examined
- Strong contextual influences may have masked variance attributable to individual behaviours

INTRODUCTION

With aging, life's hazards and rewards amass and become embodied in ways that diminish or protect health. Differences in health trajectories are the product of cumulative risk and protective factors that are programmed into biobehavioural regulatory systems.[1] The cardio-metabolic pathologies commonly-observed in older adults (partially) reflect the collective burden exacted on their bodies as they adapt to life's challenges.[2] The types and magnitude of challenges that bodies are exposed to vary across societies and time, as these reflect underlying social orders with regards to the distribution of economic, political and social resources.[2] Research that purposefully compares populations of older adults across heterogeneous societies may inform our understanding of modifiable social and behavioural factors that influence the dysregulation of biological systems. Of importance, social norms and patterning are capable of creating toxic or protective clusters that manifest among identifiable subgroups.[3] Such information is useful for directing public health interventions and for considering how contextual conditions render groups particularly vulnerable.

Metabolic syndrome (MetS) is a highly prevalent health condition amongst older adults; it confers an approximate 2-fold increased risk of cardiovascular disease and 5-fold increased risk of diabetes.[4] It entails a constellation of components including obesity, impaired glucose metabolism, hypertension, and atherogenic dyslipidaemia.[4] In older adults, MetS varies considerably across populations. In the United States and Europe, MetS prevalence is estimated at 30% [4, 5]; in urban China researchers estimate a prevalence of 60%.[6] Studies of older adults frequently document greater prevalence in women compared to men.[6-8] Heterogeneity in MetS prevalence likely reflects complex, contextually-specific risk admixtures.

Epidemiological research on aging explicitly acknowledges that environmental, social, psychological, and biological systems *interact* to influence health outcomes.[1, 3] The well-known ecological model posits that patterns of health are affected by a dynamic interplay among these factors across the life-course.[2, 9] A challenge for epidemiologists, especially with modest sample sizes, is to operationalize models that assume the joint effects of multiple risk factors on health conditions, such as MetS.[10]

Recursive partitioning is a technique that allows for exploration of distinct mixtures, or clusters, of individuals that have a particular outcome. Based on a set of candidate independent variables, it can produce classification trees with a series of binary splits highlighting subgroups with relatively similar risk profiles for a given outcome.[11, 12] The classification trees depict the joint effects of multiple risk factors.[12] It is a data-driven approach with the potential to identify complex interactions worthy of future investigation.[12] Researchers have applied partitioning techniques to identify high-risk subgroups for cardiovascular disease, diabetes, and falls in population-based studies.[13-15] Most of this work examines clinical or genetic risk factors, but the same technique can be expanded to examine social and behavioural risk factors.

In an international, multi-site cohort of community-dwelling older adults, we apply recursive partitioning to investigate social and behavioural risk factors for MetS and its components. Our objectives are to assess if there are social/behavioural risks clusters for those with MetS, or the components of the syndrome, and whether these risk clusters vary across societies. To date, we know of no other studies employing recursive-partitioning techniques to investigate predictors of MetS that are informed by a social epidemiological perspective.

METHODS

Data source and study populations

This is an analysis of 2012 baseline data from the International Mobility in Aging Study (IMIAS). IMIAS is composed of community-dwelling older adults, 65-74 years of age. This study comprises three sites in middle-income countries- Tirana (Albania), Natal (Brazil), and Manizales (Colombia)- and two from a high-income country- Kingston (Ontario, Canada) and Saint-Hyacinthe (Quebec, Canada). These cities represent diverse ways of living in distinct societies, providing a wide range of risk factors and outcomes. For example, Tirana is the capital of an ex-communist country in rapid transition to capitalism, while Manizales is in the Andean coffee-growing region, of Catholic tradition, and relatively affluent. Approximately 200 men and women, each, were recruited per site for a sample size of 2002. A detailed description of the study sites and cohort is available elsewhere.[16]

Recruitment

In Tirana, Manizales and Natal, we recruited participants through their neighbourhood primary care centres by selecting a random sample of older adults registered at each.[16] The response rate was over 90%.[16] Ethics' committees in Canada prohibited researchers directly contacting potential participants. Invitations to participate in the project were therefore sent indirectly via family physicians.[16] Thirty per cent of people receiving a letter of invitation from their doctor in Kingston and St. Hyacinthe contacted the IMIAS research team; 95% agreed to participate.[16] Comparison with 2006 Canadian census data suggests participants in Kingston were more educated than the general population of that city, while participants from St. Hyacinthe had similar educational levels to inhabitants of that city. Otherwise, characteristics between those recruited and the sampling frame were very similar.[16] At all sites, over 80% of older adults were registered at a health centre or had a primary care physician;[16] it is unlikely that our recruitment strategy systematically excluded a large segment of older adult population.

Exclusion Criterion

Those with four or more errors on the orientation scale of the Leganes Cognitive Test;[17] low scores indicate inability to complete study procedures.

Measurements

Study procedures were carried out at the participant's home, in the local language, by a trained interviewer. Detailed descriptions of data collection procedures are provided elsewhere.[16]

Metabolic syndrome

Except for the measure of insulin resistance, we defined MetS according to the Adult Panel Treatment III (ATP III) criteria.[18] IMIAS did not collect fasting glucose and the corresponding glycosylated haemoglobin (HbA1c) value was used instead.[19] Thus, MetS was defined as the presence of three or more of the following: abdominal obesity measured by waist circumference (women >88cm; men >102cm); elevated triglycerides (≥150mg/dL); low high-density lipoprotein cholesterol (HDL-C men <40mg/dL; HDL-C women <50mg/dL); elevated HbA1c (≥5.7%); and high blood pressure (≥135 mmHg systolic and/or ≥85 mmHg diastolic).

Socioeconomic and demographic characteristics

We categorized education as: less than secondary school and/or illiterate, some secondary school to completed secondary school, and post-secondary education. A participant's living arrangements were determined with the following questions: Do you live alone (Yes/No)? (If no) Who do you live with? Responses were then categorized as: Alone, spouse only, and multiple people.

We determined exposure to childhood social and economic adversity with a scale that varied from zero to three including parental alcohol or drug abuse, witnessing family physical violence, and having been physically abused (childhood social adversity); poor economic status, hunger, and parental unemployment (childhood economic adversity).[20] Occupation was grouped into five categories: non-manual, service, agriculture, manual, and housewife, according to self-reported longest held occupation (based on International Labour Organization categories). We enquired about current annual income levels. Based on the annual minimum salary for each site, individuals were categorized as poor, middle, upper middle, and high income. For example, in Canada, the minimum salary is $19680CAN/year. Thus, we categorized Canadian participants as poor if they earned less than $20000CAN/year. Those who earned more than the minimum salary but less than twice it ($20-39, 999) were classified as middle income, while those that earned twice or greater the minimum salary, but less than three times it, were classified as upper-middle ($40-59,999), and those that earned 3 times or more the minimum salary (≥$60, 000) were classified as upper-income. This was done for each site based on the site-specific minimum salary. Income sufficiency was assessed according: To what extent does your income allow you to meet your needs? Responses were categorized into: Very sufficient, sufficient, and not (at all) sufficient. We asked participants about their work history in the past two weeks and categorized them as:

worked with remuneration; worked without remuneration; had a job, but did not work; retired or pensioned; and did not work. We also asked participants if they currently smoke. Responses were categorized as regular, occasional, used to be a smoker, and never. Finally, we assessed minutes of physical activity per week with a validated computer-animated assessment tool.[21]

Statistical analysis

Descriptive statistics summarize overall sample characteristics. Because the distributions were positively skewed for some measures, we report the median, first and third quartiles for all continuous variables. We performed Chi-square tests to investigate the associations between MetS and categorical independent variables and carried out two-sample t-tests to examine mean differences in biomarkers. Random Forest method was used to impute missing physical activities (n=59).[22]

Model-based recursive partitioning method (MOB) was applied to cluster individuals into subgroups with similar response values.[23] Recursive partitioning creates a decision tree that classifies members of the population by splitting it into subpopulations based on independent (partitioning) variables. The process is termed recursive because each sub-population may be split a number of times until a particular stopping criterion is reached. Our stopping criteria were: 5% level of significance and minimum sample size of 100 at terminal nodes.

Traditional implementations of recursive partitioning algorithms are known as Classification and Regression Trees (CART).[10] MOB integrates parametric statistical models into classification trees.[23] A parametric model (e.g., logistic regression for MetS vs. a control variable age) is tested for parameter instability over a set of partitioning variables. If there is some overall parameter variability, the model is split with respect to the variable with the highest instability (i.e. the smallest p-value), while controlling for age. For continuous partitioning variables, MOB tests and selects an optimal cut-off point and split subjects into two subgroups.[23-25] The outcome is a tree where each node is associated with a fitted parametric model (i.e., logistic regression model of Mets vs. age) that can be visualized and summarized. If the outcome variable is quantitative, linear models are applied.

We performed MOB for MetS, systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, log transformed triglyceride, HDL-C, and HbA1c, controlling for age. The partitioning variables included social and behavioural risk characteristics described previously. Statistical software R (version 3.2.2) and the R package "party" were used.

RESULTS

Complete data on all variables were available for 1628 (81%) participants. Table 1 presents the frequency of MetS according to the participant characteristics. MetS was observed in 43% participants, 50% of women and 35% of men. For most variables, there were important differences in the proportion of participants with MetS. It concentrated among those of lower socioeconomic status: those with lower education, lower incomes, manual workers and housewives. More MetS was observed among those reporting childhood adversities. Those with MetS reported had greater mean blood pressure, waist circumference, HbA1c, triglyceride, low HDL measures, and walked less on average than those without it.

---Insert table 1 here (see next page)---

Table 1: Descriptive characteristics of the participants and frequency of metabolic syndrome.

	Overall (N=1628)	Metabolic Syndrome Yes (42.7%)	No (57.3%)	*p-value**
	N (%)	N (%)	N (%)	
Site				
Kingston	289(17.8%)	92(31.8%)	197(68.2%)	<.0001
St. Hyacinthe	310(19.0%)	96(31.0%)	214(69.0%)	
Tirana	344(21.1%)	171(49.7%)	173(50.3%)	
Manizales	374(23.0%)	172(46.0%)	202(54.0%)	
Natal	311(19.1%)	164(52.7%)	147(47.3%)	
Sex				
Female	844(51.8%)	424(50.2%)	420(49.8%)	<.0001
Male	784(48.2%)	271(34.6%)	513(65.4%)	
Educational Attainment				
Primary / illiterate	760(46.7%)	366(48.2%)	394(51.8%)	0.0001
Secondary	217(13.3%)	91(41.9%)	126(58.1%)	
Post-secondary	651(40.0%)	238(36.6%)	413(63.4%)	
Current Living Arrangements				
Alone	254(15.6%)	100(39.4%)	154(60.6%)	0.0001
Spouse only	609(37.4%)	225(36.9%)	384(63.1%)	
Other	765(47.0%)	370(48.4%)	395(51.6%)	
Adult Occupation				
Non manual	593(36.4%)	211(35.6%)	382(64.4%)	<.0001
Service	160(9.8%)	67(41.9%)	93(58.1%)	
Agriculture	94(5.8%)	41(43.6%)	53(56.4%)	
Manual	607(37.3%)	274(45.1%)	333(54.9%)	
Housewife	174(10.7%)	102(58.6%)	72(41.4%)	
Current Income				
Poor	417(25.6%)	189(45.3%)	228(54.7%)	0.001
Middle	704(43.2%)	315(44.7%)	389(55.3%)	
Upper middle	346(21.3%)	145(41.9%)	201(58.1%)	
High	161(9.9%)	46(28.6%)	115(71.4%)	
Perceived Income Sufficiency				
Very sufficient	339(20.8%)	102(30.1%)	237(69.9%)	<.0001
Sufficient	537(33.0%)	215(40.0%)	322(60.0%)	
Not (at all) sufficient	752(46.2%)	378(50.3%)	374(49.7%)	
Childhood Economic Adversity				
No adversities	858(52.7%)	351(40.9%)	507(59.1%)	0.0291
One adversity event	453(27.8%)	186(41.1%)	267(58.9%)	
Two adversity events	212(13.0%)	102(48.1%)	110(51.9%)	
Three adversity events	105(6.4%)	56(53.3%)	49(46.7%)	
Childhood Social Adversity				
No adversities	1, 231(75.6%)	505(41.0%)	726(59.0%)	0.0792
One adversity event	245(15.0%)	113(46.1%)	132(53.9%)	
Two adversity events	119(7.3%)	59(49.6%)	60(50.4%)	
Three adversity events	33(2.0%)	18(54.5%)	15(45.5%)	

Table 1 (continued): Descriptive characteristics of the participants.

	Overall (N=1628)	Metabolic Syndrome Yes (42.7%)	No (57.3%)	*p-value**
	N (%)	N (%)	N (%)	
Smoker				
Regular	138(8.5%)	64(46.4%)	74(53.6%)	0.109
Occasional	37(2.3%)	18(48.6%)	19(51.4%)	
Used to be	676(41.5%)	265(39.2%)	411(60.8%)	
Never	777(47.7%)	348(44.8%)	429(55.2%)	
Current Employment Status				
Worked with remuneration	185(11.4%)	66(35.7%)	119(64.3%)	0.011
Worked w/o remuneration	201(12.3%)	105(52.2%)	96(47.8%)	
Had a job, but did not work	25(1.5%)	9(36.0%)	16(64.0%)	
Retired or Pensioned	1, 119(68.7%)	468(41.8%)	651(58.2%)	
Did not work	98(6.0%)	47(48.0%)	51(52.0%)	
	Median(Q1, Q3)	Median(Q1, Q3)	Median(Q1, Q3)	
Age (year)	69(67, 72)	69 (67, 72)	69 (67, 71)	0.0451
Physical Activity (minutes/week)	20(9, 39)	15 (6, 32)	24(10, 43)	<.0001
SBP (mmHg)	138(126, 152)	143(134, 157)	132(122, 146)	<.0001
DBP (mmHg)	79 (71, 86)	81(74, 88)	77(70, 84)	<.0001
Waist (cm)	96(88, 104)	101(94, 108)	92(85, 100)	<.0001
HbA1c (%)	5.8(5.5, 6.2)	6.1(5.8, 6.6)	5.7(5.4, 6.0)	<.0001
Triglyceride (mg/dL)	126(91, 172)	165(125, 211)	105 (78, 134)	<.0001
HDL (mg/dL)	50(43, 60)	45(39, 53)	55(47, 63)	<.0001

**p-values:* obtained from Chi-square tests of association between MetS (Yes/No) and categorical explanatory variables, and t-tests for difference in MetS (Yes/No) for continuous variable

Table 2 presents participant characteristics by study site and shows a notably greater frequency of MetS among participants from the middle-income sites (46-53%) compared to those from the Canadian sties (≈30%).

---Insert table 2 here (see next page)---

Table 2: Descriptive characteristics of the participants by study site.

	Kingston	St. Hyacinthe	Tirana	Manizales	Natal
	289(17.8%)	310(19%)	344(21.1%)	374(23%)	311(19.1%)
	N (%)	N (%)	N (%)	N (%)	N (%)
Metabolic Syndrome					
Yes	92(31.8%)	96(31.0%)	171(49.7%)	172(46.0%)	164(52.7%)
No	197(68.2%)	214(69.0%)	173(50.3%)	202(54.0%)	147(47.3%)
Sex					
Female	152(52.6%)	166(53.5%)	178(51.7%)	190(50.8%)	158(50.8%)
Male	137(47.4%)	144(46.5%)	166(48.3%)	184(49.2%)	153(49.2%)
Educational Attainment					
Primary / illiterate	29(10.0%)	85(27.4%)	54(15.7%)	310(82.9%)	282(90.7%)
Secondary	37(12.8%)	67(21.6%)	79(23.0%)	19(5.1%)	15(4.8%)
Post-secondary	223(77.2%)	158(51.0%)	211(61.3%)	45(12.0%)	14(4.5%)
Current Living Arrangements					
Alone	88(30.4%)	72(23.2%)	31(9.0%)	47(12.6%)	16(5.1%)
Spouse only	127(43.9%)	201(64.8%)	151(43.9%)	68(18.2%)	62(19.9%)
Other	74(25.6%)	37(11.9%)	162(47.1%)	259(69.3%)	233(74.9%)
Adult Occupation					
Non manual	226(78.2%)	158(51.0%)	116(33.7%)	63(16.8%)	30(9.6%)
Service	24(8.3%)	40(12.9%)	23(6.7%)	22(5.9%)	51(16.4%)
Agriculture	2(0.7%)	18(5.8%)	5(1.5%)	37(9.9%)	32(10.3%)
Manual	27(9.3%)	78(25.2%)	199(57.8%)	161(43.0%)	142(45.7%)
Housewife	10(3.5%)	16(5.2%)	1(0.3%)	91(24.3%)	56(18.0%)
Current Income					
Poor	51(17.6%)	109(35.2%)	36(10.5%)	191(51.1%)	30(9.6%)
Middle	97(33.6%)	122(39.4%)	204(59.3%)	112(29.9%)	169(54.3%)
Upper middle	61(21.1%)	62(20.0%)	82(23.8%)	50(13.4%)	91(29.3%)
High	80(27.7%)	17(5.5%)	22(6.4%)	21(5.6%)	21(6.8%)
Perceived Income Sufficiency					
Very sufficient	174(60.2%)	132(42.6%)	5(1.5%)	19(5.1%)	9(2.9%)
Sufficient	101(34.9%)	157(50.6%)	121(35.2%)	89(23.8%)	69(22.2%)
Not (at all) sufficient	14(4.8%)	21(6.8%)	218(63.4%)	266(71.1%)	233(74.9%)
Childhood Economic Adversity					
No adversities	190(65.7%)	201(64.8%)	147(42.7%)	216(57.8%)	104(33.4%)
One adversity event	73(25.3%)	92(29.7%)	89(25.9%)	108(28.9%)	91(29.3%)
Two adversity events	24(8.3%)	15(4.8%)	75(21.8%)	28(7.5%)	70(22.5%)
Three adversity events	2(0.7%)	2(0.6%)	33(9.6%)	22(5.9%)	46(14.8%)
Childhood Social Adversity					
No adversities	210(72.7%)	229(73.9%)	281(81.7%)	287(76.7%)	224(72.0%)
One adversity event	42(14.5%)	54(17.4%)	27(7.8%)	63(16.8%)	59(19.0%)
Two adversity events	25(8.7%)	22(7.1%)	30(8.7%)	18(4.8%)	24(7.7%)
Three adversity events	12(4.2%)	5(1.6%)	6(1.7%)	6(1.6%)	4(1.3%)

Table 2 (continued): Descriptive characteristics of the participants by study site.

	Kingston	**St. Hyacinthe**	**Tirana**	**Manizales**	**Natal**
	289(17.8%)	310(19%)	344(21.1%)	374(23%)	311(19.1%)
Smoker					
Regular	14(4.8%)	19(6.1%)	43(12.5%)	37(9.9%)	25(8.0%)
Occasional	3(1.0%)	5(1.6%)	12(3.5%)	13(3.5%)	4(1.3%)
Used to be	141(48.8%)	169(54.5%)	81(23.5%)	147(39.3%)	138(44.4%)
Never	131(45.3%)	117(37.7%)	208(60.5%)	177(47.3%)	144(46.3%)
Current Employment Status					
Worked with remuneration	43(14.9%)	39(12.6%)	8(2.3%)	58(15.5%)	37(11.9%)
Worked w/o remuneration	8(2.8%)	18(5.8%)	8(2.3%)	99(26.5%)	68(21.9%)
Had a job, but did not work	8(2.8%)	2(0.6%)	4(1.2%)	8(2.1%)	3(1.0%)
Retired or Pensioned	228(78.9%)	246(79.4%)	323(93.9%)	133(35.6%)	189(60.8%)
Did not work	2(0.7%)	5(1.6%)	1(0.3%)	76(20.3%)	14(4.5%)
	Median(Q1,Q3)	Median (Q1,Q3)	Median(Q1,Q3)	Median(Q1,Q3)	Median(Q1,Q3)
Age (year)	69(67, 71)	68(67, 71)	70(66, 72)	69(67, 72)	69(67, 71)
Physical Activity (minutes/wk)	26(9, 51)	24(9, 39)	27(11, 48)	17(9, 39)	10(4, 23)
SBP (mmHg)	135(124, 145)	134(125, 143)	144(130, 161)	133(123, 146)	146(130, 161)
DBP (mmHg)	77(71, 83)	75(68, 81)	84(75, 91)	79(72, 86)	78(71, 86)
Waist (cm)	96(88, 107)	94(87, 102)	102(95, 107)	90(83, 96)	100(93, 106)
HbA1c (%)	5.8(5.5, 6.0)	5.8(5.5, 6.1)	5.6(5.3, 6.3)	5.9(5.7, 6.2)	6.0(5.6, 6.5)
Triglyceride (mg/dL)	88(60, 136)	122(91, 159)	130(106, 165)	140(106, 201)	131(97, 187)
HDL (mg/dL)	54(45, 66)	56(46, 67)	47(41, 52)	48(39, 57)	52(47, 61)

Figure 1 depicts the MOB tree for MetS. The highest values of MetS were observed in clusters of women from the middle-income study sites (Tirana, Manizales, Natal). In these clusters, the predicted proportion with MetS varied from 58 to 68%, depending on education. Better-educated women from these sites had more MetS. Among women from the Canadian sites, less walking time per week distinguished the higher from lower probability cluster. The lowest predicted proportion (26%) of MetS was observed in men with post-secondary education reporting no childhood social adversities, and in women from the Canadian sites who had more walking time per week.

---Insert Figure 1 here---

The supplementary files contain the MOB trees for MetS components. Each tree depicts unique clusters that do not correspond with those observed for MetS as a whole. For example, the greatest estimated mean systolic blood pressure (154 mmHg) was observed among participants from Tirana and Natal, with income insufficiency, and who smoked regularly or used to. For this outcome, in contrast to MetS as a whole, sex was not a partitioning variable. Overall, in all models except HDL, study site was the primary partitioning variable and in some cases (triglycerides), the only one. Typically, participants from Natal and Tirana had unfavourable estimates for MetS components; however, participants from Manizales had the greatest estimated triglyceride concentrations (145 mg/dL). Participant sex was a key partitioning variable for DBP, waist circumference, and HDL concentration. Other partitioning variables for one or two of the MetS components included: weekly walking time, current employment status, perceived income sufficiency, living arrangements, smoking, adult occupation, and current income.

DISCUSSION

The MOB technique identified distinct clusters of individuals with differential probabilities of MetS and its components, according to multiple social and behavioural risk factors. For the syndrome as a whole, in clusters of women from middle-income sites, the predicted proportion with MetS was quite high (58-68%). In clusters of men, the predicted proportion with MetS was lower (26-41%)

and highest among men reporting childhood social adversities. MetS in women from the Canadian sites varied considerably based on average walking time per week. Women from Kingston and St. Hyacinthe who walked minimally (>11 min/week) had predicted probabilities of MetS identical to men with post-secondary education and no childhood social adversities. This work demonstrates the potential of using MOB to identify joint effects in a moderately-sized sample of individuals. It raises questions for future investigation, especially related to the concentration of risk(s) in certain subgroups.

This study corroborates previous findings that the prevalence of MetS varies according to age, sex, and socioeconomic status.[4, 26, 27] Consistent with other studies, we observed a concentration of MetS in participants of lower socioeconomic status.[27-29] When applying MOB, we observed distinct risk clusters according to study site and participant sex, education and childhood adversity. These findings support a dynamic interplay between contextual and social risk factors and the concentration of risks in certain subgroups, which is consistent with the notion of vulnerable populations proposed by Frohlich and Potvin.[3] Accordingly, vulnerable populations are defined by shared social characteristics that put them at “higher risk of risks”.[3 pp218] These risks and their accumulation across the life-course relate to fundamental causes linked to one’s social position within the predominant social structure.[3] This may explain why study site and sex were key partitioning variables. Study site proxies societal opportunities for education, occupation, and income and expectations surrounding behaviours and diet. The clustering by site supports research underscoring the importance of context in patterning the risk exposures of individuals.[3, 30] Sex/gender likely underpins access to resources such as money, knowledge and power affecting health outcomes through multiple risk factors.[31]

In studies with large sample sizes (>10, 000 participants), complex joint-effects have been observed with traditional regression analysis techniques. For example, using data from representative samples of United States' adults aged 25 and older, Loucks *et al.* reported that overall, the prevalence of MetS was similar in women and men, both low education and poverty were associated with MetS, and the social gradient of the prevalence of MetS was more pronounced in women than in men.[32] These United States' findings differ from ours since in IMIAS, sex was the first stratifying variable, with an overall higher frequency of MetS in women than in men. However, for both men and women in our study, education was an important predictor of MetS at most sites; although, the direction of the association between education and MetS was not consistent. Among women from the middle-income sites, greater educational attainment was associated with a greater predicted prevalence of MetS. Among men with no childhood social adversity, low educational attainment was associated to a greater predicted prevalence of MetS.

When MOB was applied to the syndrome components, only study site and participant sex were consistent partitioning variables for most components. In general, when measures of socioeconomic status were partitioning variables, lower status was associated with poorer outcomes. For example, income insufficiency predicted higher mean diastolic blood pressure among Tirana participants. Measures of socioeconomic status appeared as partitioning variables more frequently than risk behaviours. This is consistent with recent work analysing individual-level data from more than 1.7 million people in which low socioeconomic status was associated with premature mortality across multiple disease categories and ranked 3rd in population attributable fraction for mortality among a large list of risk factors (physical inactivity ranked 2nd).[33] Greater mean weekly physical activity predicted lower waist circumferences and greater HDL concentrations, consistent with the literature.[34-36]

This study has strengths. First is the use of the MOB technique. Traditional CART methods have the vulnerability of over-fitting, selection bias and no concept of statistical significance. Thus pruning and cross-validation methods are used to avoid the over-fitting problems characteristic of CART. MOB is implemented via hypothesis tests, which leads to regression models whose predictive performance is equivalent to optimally pruned trees, therefore offering an intuitive and computationally efficient solution to the over-fitting problem, and the resulting models are easier to communicate to practitioners.[23, 37]

This study has limitations. Study site and sex are structuring variables that may mask more proximal risk factors for disease. Individual risk behaviours, such as smoking, may be ubiquitous within certain subgroups,[30] rendering it difficult to detect the influence of these behaviours on MetS using the MOB technique. Another limitation is that we used a single waist circumference cut-off value for all populations. Arguments exist for country and/or ethnicity-specific waist circumference cut-offs, but more work is required to optimally determine these.[38] Finally, we did not collect individual dietary data or data on the early nutritional environment.[39]

Conclusion

We applied a recursive partitioning technique to investigate risk clustering for MetS in an international, multi-site study of community-dwelling older adults and observed unique risk clusters according to mostly contextual and socioeconomic characteristics. MOB may prove informative in studies with much larger samples, such as the Health and Retirement Study, where it can be used generate new hypotheses about risk clustering and then more traditional deterministic techniques can corroborate or contradict these hypotheses. With regards to both clinical practice and health promotion activities, identifying risk clusters is important for targeting purposes, as the intensity and type of programs may differ according to sub-groups.[12]

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CONTRIBUTION STATEMENT

CMP and MVZ conceived of the study. CMP and YW analysed and interpreted the data. CMP, YW, JFG, and MVZ contributed to the writing and editing of this manuscript.

DATA SHARING

Extra data is available through registration on the IMIAS website (http://www.imias.ufrn.br). Registered users can request IMIAS data through a data request form.

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COMPETING INTERESTS

None declared

PATIENT CONSENT

Written informed consent was obtained from all IMIAS participants.

FIGURE 1

Model based recursive partitioning for metabolic syndrome controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean proportions of metabolic syndrome obtained from logistic regression models by age. The predicted mean proportion of metabolic syndrome and 95% confidence interval for each terminal node are listed under the plots.

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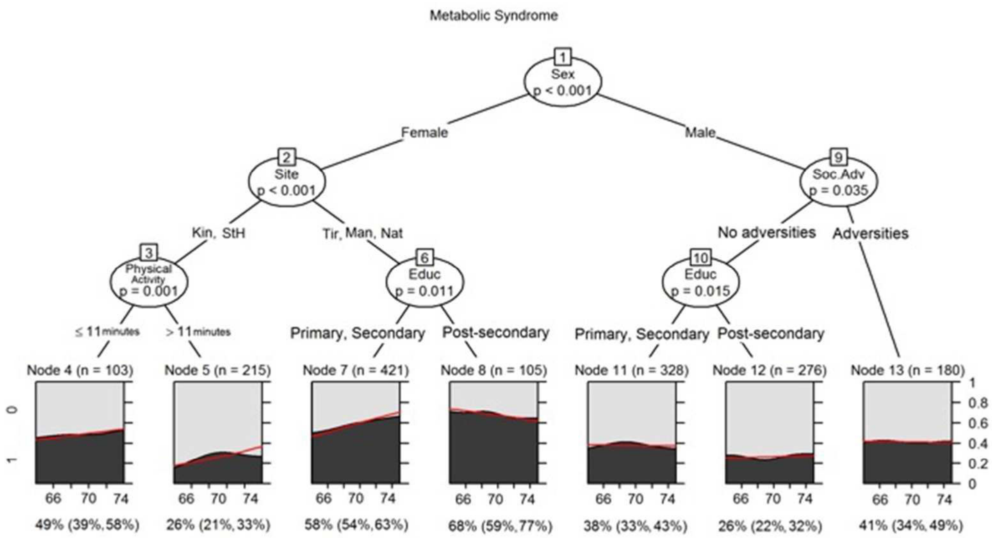

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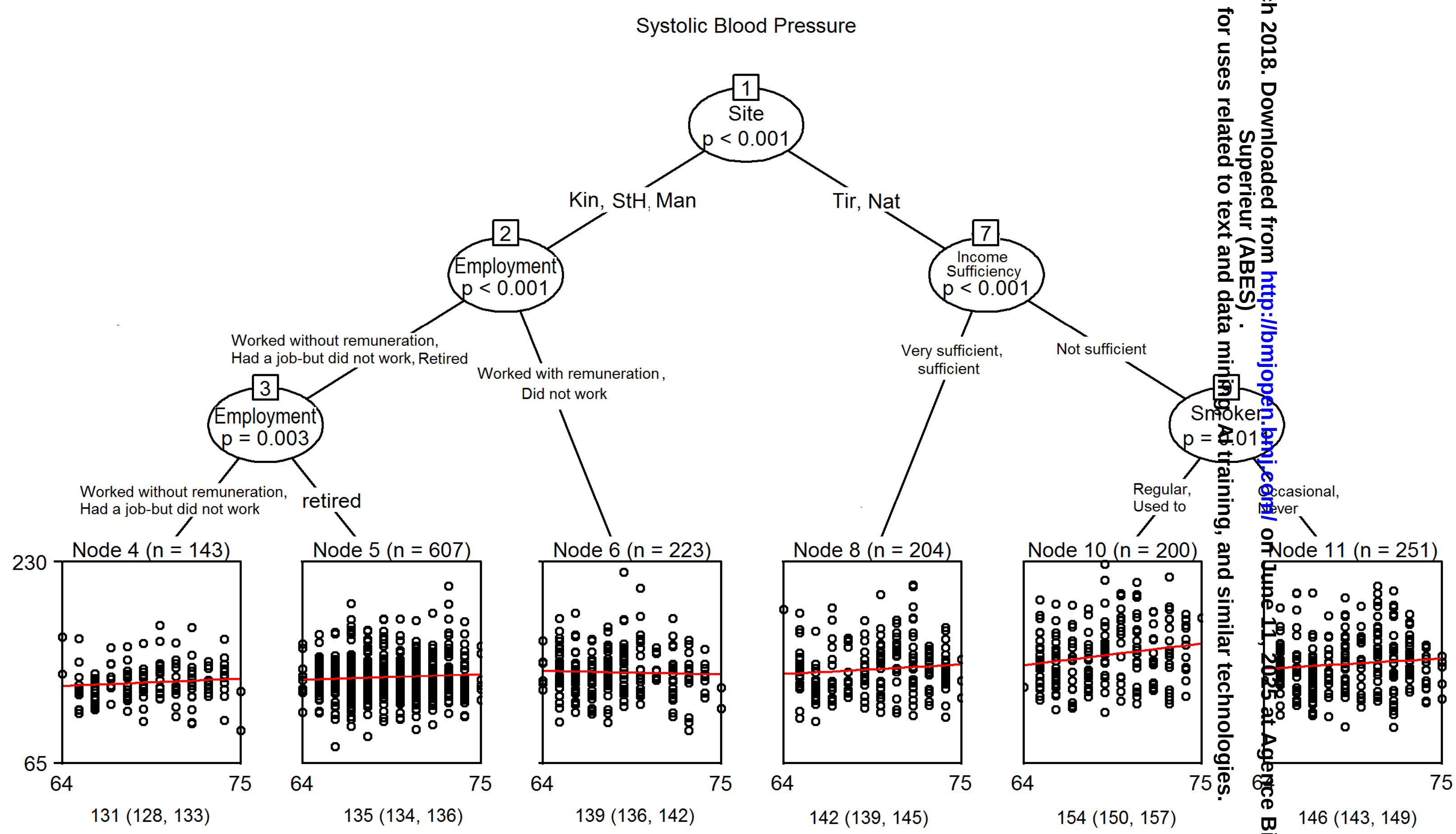
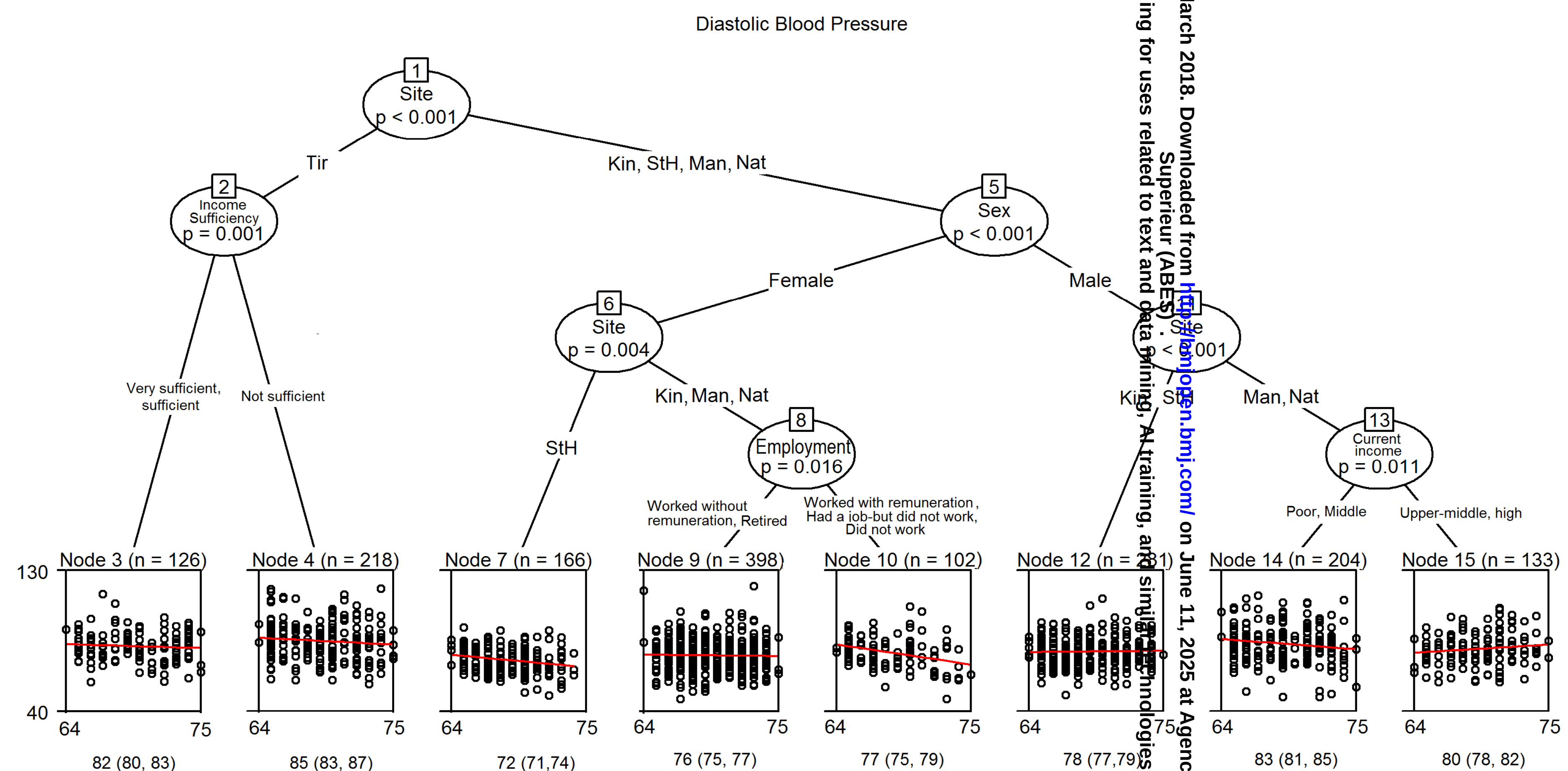
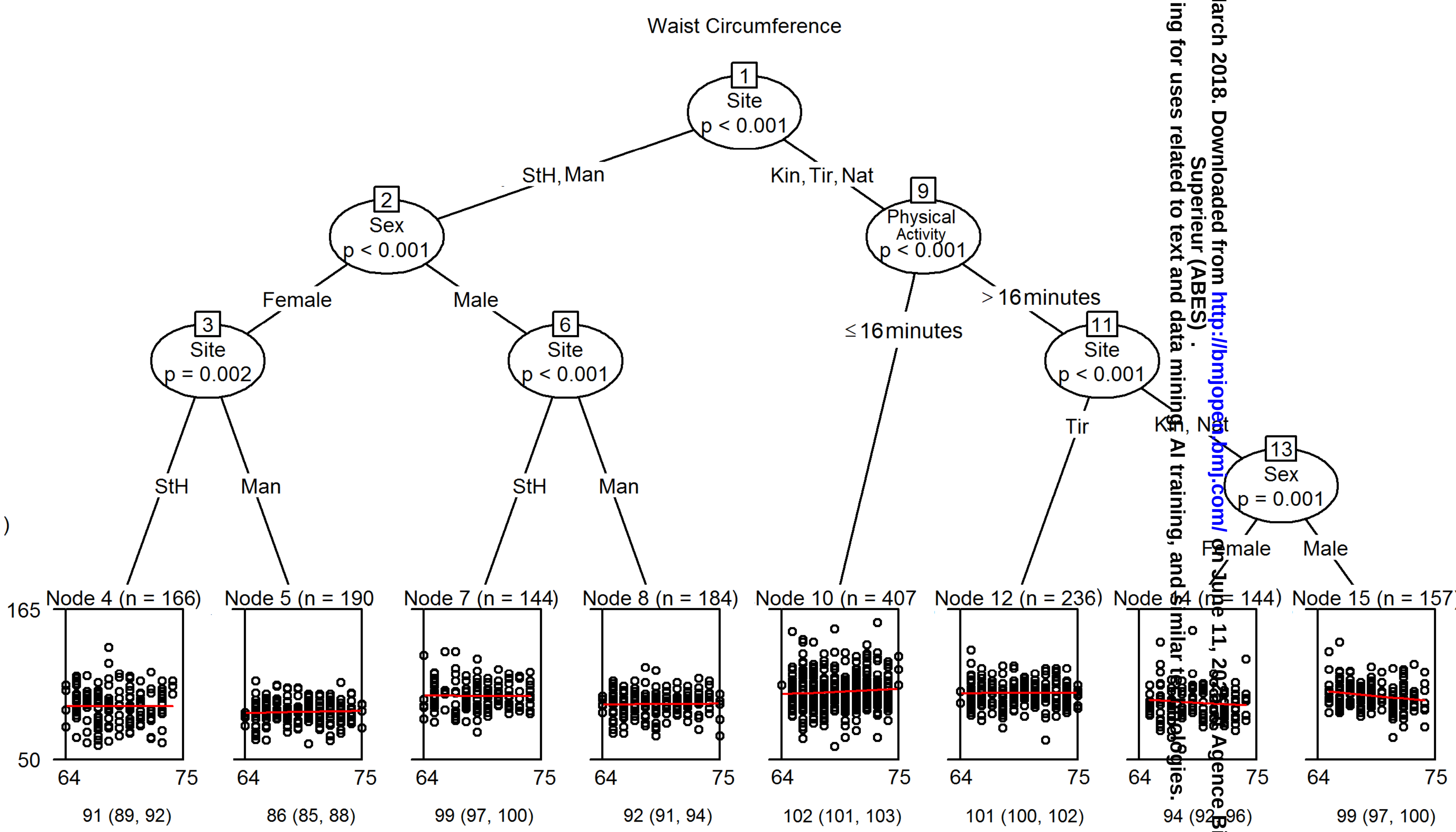


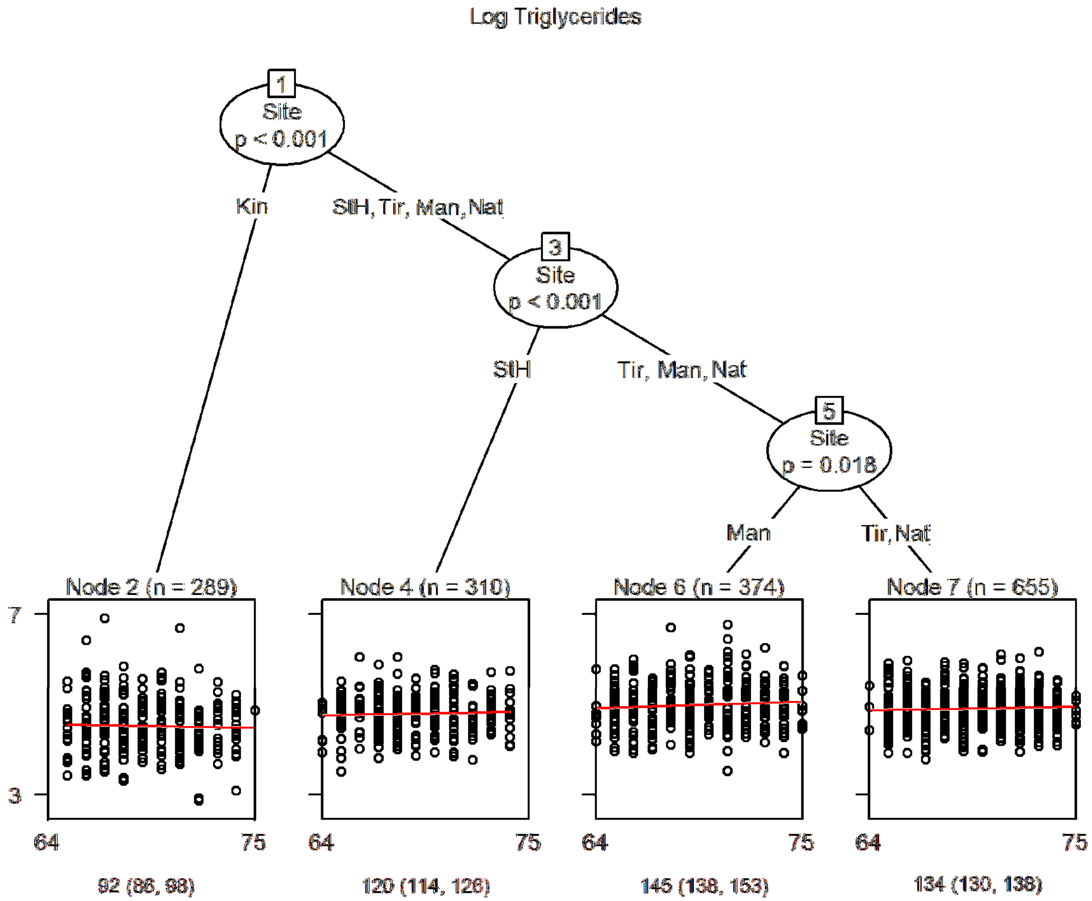
Supplemental figure 1. Model based recursive partitioning for systolic blood pressure (SBP) controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean SBP obtained from linear regression models by age. The predicted mean SBP and 95% confidence interval for each terminal node are listed under the plots.



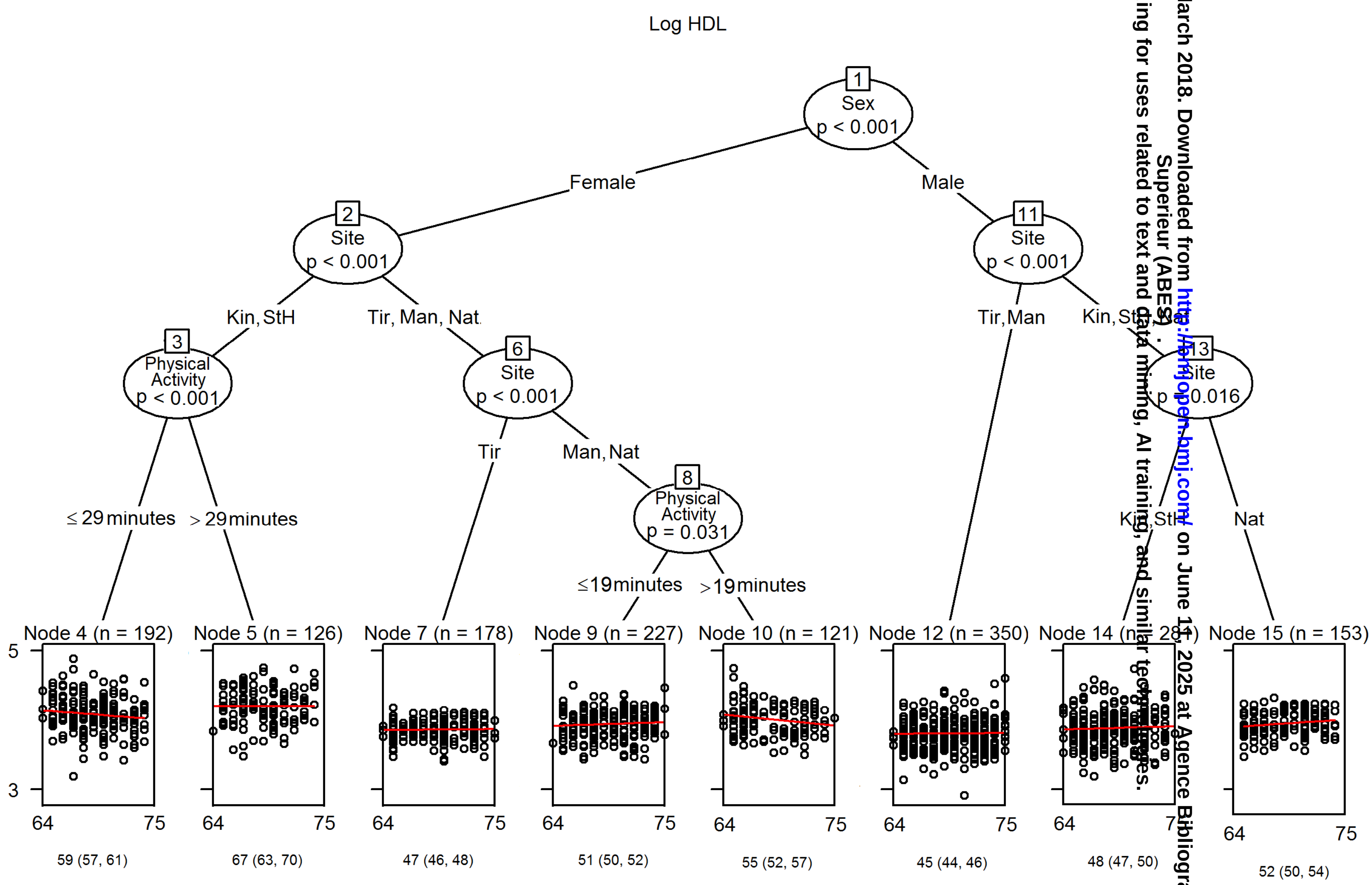
Supplemental figure 2. Model based recursive partitioning for diastolic blood pressure (DBP) controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean DBP obtained from linear regression models by age. The predicted mean DBP and 95% confidence interval for each terminal node are listed under the plots.



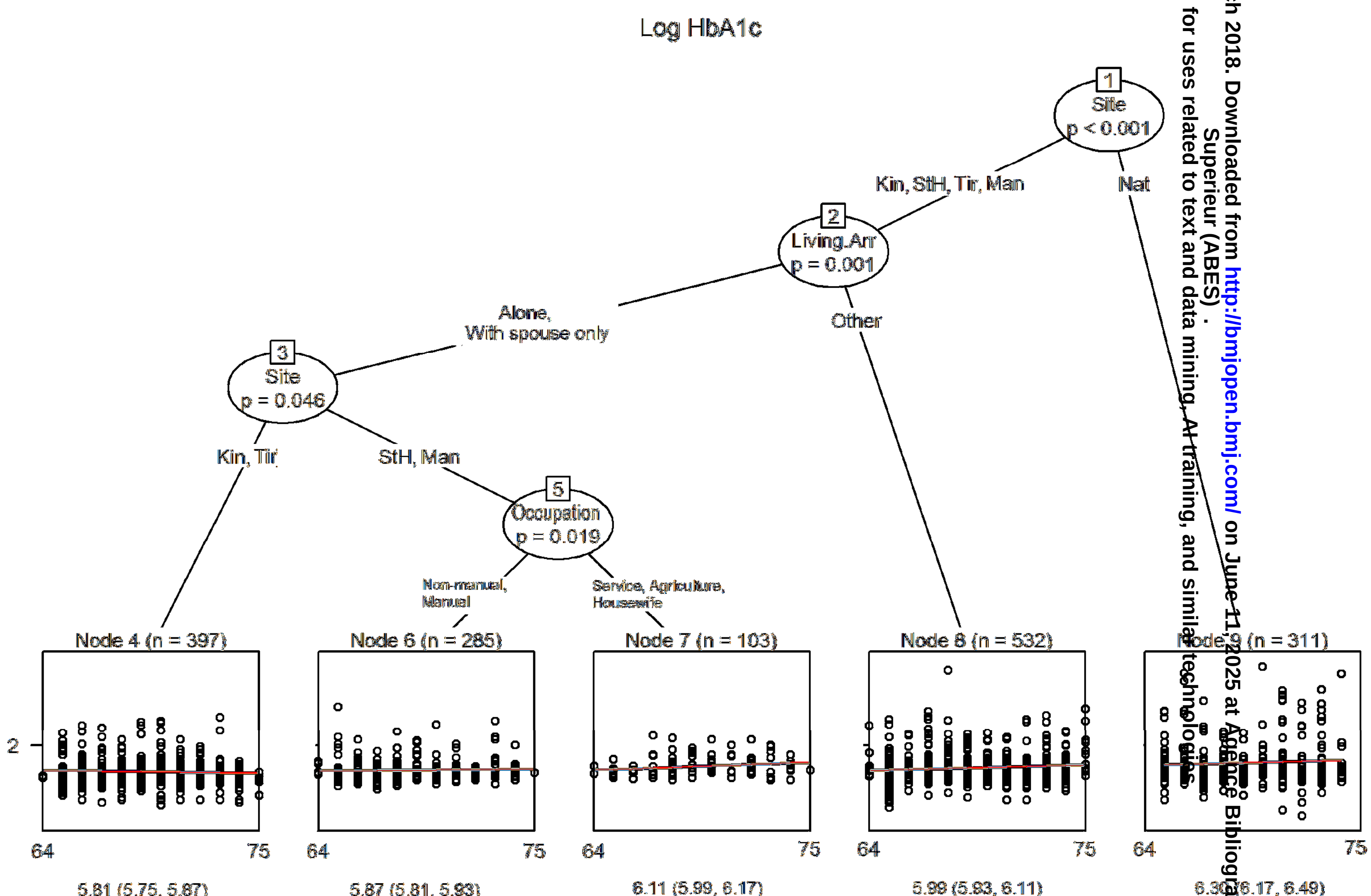
Supplemental figure 3. Model based recursive partitioning for waist circumference (WC) controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean WC obtained from linear regression models by age. The predicted mean WC and 95% confidence interval for each terminal node are listed under the plots.



Supplemental figure 4. Model based recursive partitioning for log triglycerides controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean triglycerides obtained from linear regression models by age. The back transformed triglycerides and 95% confidence interval for each terminal node are listed under the plots.



Supplemental figure 5. Model based recursive partitioning for log HDLs controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean HDL obtained from linear regression models by age. The back transformed HDL and 95% confidence interval for each terminal node are listed under the plots.



Supplemental figure 6. Model based recursive partitioning for log Hba1c controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean Hba1c obtained from linear regression models by age. The back transformed Hba1c and 95% confidence interval for each terminal node are listed under the plot.

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Model-based recursive partitioning to identify risk clusters for metabolic syndrome and its components: Findings from the International Mobility in Aging Study

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Title: Model-based recursive partitioning to identify risk clusters for metabolic syndrome and its components: Findings from the International Mobility in Aging Study

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ABSTRACT

Objective: Conceptual models underpinning much epidemiological research on aging acknowledge that environmental, social, and biological systems *interact* to influence health outcomes. Recursive partitioning is a data-driven approach that allows for concurrent exploration of distinct mixtures, or clusters, of individuals that have a particular outcome. Our aim is to use recursive partitioning to examine risk clusters for metabolic syndrome (MetS) and its components, in order to identify vulnerable populations.

Study Design: Cross-sectional analysis of baseline data from a prospective longitudinal cohort called the International Mobility in Aging Study (IMIAS).

Setting: IMIAS includes sites from three middle-income countries- Tirana (Albania), Natal (Brazil), and Manizales (Colombia)- and two from Canada- Kingston (Ontario) and Saint-Hyacinthe (Quebec).

Participants: Community-dwelling male and female adults, ages 64 to 75 (N=2002).

Primary and Secondary Outcome Measures: We apply recursive partitioning to investigate social and behavioural risk factors for MetS and its components. Model-based recursive partitioning (MOB) was used to cluster participants into age-adjusted risk groups based on variabilities in: study site, sex, education, living arrangements, childhood adversities, adult occupation, current employment status, income, perceived income sufficiency, smoking status, and weekly minutes of physical activity.

Results: 43% of participants had MetS. Using MOB, the primary partitioning variable was participant sex. Among women from middle-incomes sites, the predicted proportion with MetS ranged from 58 to 68%. Canadian women with limited physical activity had elevated predicted proportions of MetS (49%, 95%CI 39-58%). Among men, MetS ranged from 26% to 41% depending on childhood social adversity and education. Clustering for MetS components differed from the syndrome and across components. Study site was a primary partitioning variable for all components except HDL cholesterol. Sex was important for most components.

Conclusion: MOB is a promising technique for identifying disease risk clusters (e.g. vulnerable populations) in modestly sized samples.

Key words: Recursive partitioning; Metabolic syndrome; Older adults; Global health

ARTICLE SUMMARY

Strengths and limitations of this study

- Explores social and behavioural risk clustering for metabolic syndrome among community-dwelling older adults from five diverse global settings
- Applies model-based recursive partitioning, which is more intuitive and computationally efficient than Classification and Regression Trees (CART), to identify risk clusters
- Provides an example of how model-based recursive partitioning can be used in a modestly-sized sample for hypothesis generation about complex admixtures of risk factors
- Lacks data on participant diet, which likely clusters with many of the social and behavioural factors examined
- Strong contextual influences may have masked variance attributable to individual behaviours

INTRODUCTION

With aging, life's hazards and rewards amass and become embodied in ways that diminish or protect health. Differences in health trajectories are the product of cumulative risk and protective factors that are programmed into biobehavioural regulatory systems.[1] The cardio-metabolic pathologies commonly-observed in older adults (partially) reflect the collective burden exacted on their bodies as they adapt to life's challenges.[2] The types and magnitude of challenges that bodies are exposed to vary across societies and time, as these reflect underlying social orders with regards to the distribution of economic, political and social resources.[2] Research that purposefully compares populations of older adults across heterogeneous societies may inform our understanding of modifiable social and behavioural factors that influence the dysregulation of biological systems. Of importance, social norms and patterning are capable of creating toxic or protective clusters that manifest among identifiable subgroups.[3] Such information is useful for directing public health interventions and for considering how contextual conditions render groups particularly vulnerable.

Metabolic syndrome (MetS) is a highly prevalent health condition amongst older adults; it confers an approximate 2-fold increased risk of cardiovascular disease and 5-fold increased risk of diabetes.[4] It entails a constellation of components including obesity, impaired glucose metabolism, hypertension, and atherogenic dyslipidaemia.[4] In older adults, MetS prevalence varies considerably across populations. Among older adults in the United States and Europe, MetS prevalence is estimated at 30% [4, 5]; in urban China researchers estimate a prevalence of 60%.[6] In Canada, MetS prevalence increases with chronological age; approximately 40% of adults aged 60 to 79 years were estimated to have the syndrome according to the 2007-09

Canadian Health Measures Survey. [7] Studies of older adults frequently document greater prevalence in women compared to men[6-10], but report inconsistent associations with income and education. Some document linear associations between education and MetS prevalence, with the lowest educated at highest risk [10]. Others document non-linear associations, in which the highest risk groups are lower-middle income and high school graduates, while those in the lowest income group and without a high school education are slightly protected. [7] Yet, others observe strong associations with education, but not income [10] or associations with education and income in one sex over the other [10, 11]. Heterogeneity in MetS prevalence likely reflects complex, contextually-specific risk admixtures.

Epidemiological research on aging explicitly acknowledges that environmental, social, psychological, and biological systems *interact* to influence health outcomes.[1, 3] The well-known ecological model posits that patterns of health are affected by a dynamic interplay among these factors across the life-course.[2, 12] A challenge for epidemiologists, especially with modest sample sizes, is to operationalize models that assume the joint effects of multiple risk factors on health conditions, such as MetS.[13]

Recursive partitioning is a technique that allows for exploration of distinct mixtures, or clusters, of individuals that have a particular outcome. Based on a set of candidate independent variables, it can produce classification trees with a series of binary splits highlighting subgroups with relatively similar risk profiles for a given outcome.[14, 15] The classification trees depict the joint effects of multiple risk factors.[15] It is a data-driven approach with the potential to identify complex interactions worthy of future investigation.[15] Researchers have applied partitioning techniques to identify high-risk subgroups for cardiovascular disease, diabetes, and falls in population-based studies.[16-18] Most of this work examines clinical or genetic risk factors, but the same technique can be expanded to examine social and behavioural risk factors.

In an international, multi-site cohort of community-dwelling older adults, we apply recursive partitioning to investigate social and behavioural risk factors for MetS and its components. Our objectives are to assess if there are social/behavioural risks clusters for those with MetS, or the components of the syndrome, and whether these risk clusters vary across societies. To date, we know of no other studies employing recursive-partitioning techniques to investigate predictors of MetS that are informed by a social epidemiological perspective.

METHODS

Data source and study populations

This is an analysis of 2012 baseline data from the International Mobility in Aging Study (IMIAS). IMIAS is composed of community-dwelling older adults, 65-74 years of age. This study comprises three sites in middle-income countries- Tirana (Albania), Natal (Brazil), and Manizales (Colombia)- and two from a high-income country- Kingston (Ontario, Canada) and Saint-Hyacinthe (Quebec, Canada). These cities represent diverse ways of living in distinct societies, providing a wide range of risk factors and outcomes. For example, Tirana is the capital of an ex-communist country in rapid transition to capitalism, while Manizales is in the Andean coffee-growing region, of Catholic tradition, and relatively affluent. Approximately 200 men and women, each, were recruited per site for a sample size of 2002. A detailed description of the study sites and cohort is available elsewhere.[19]

Recruitment

In Tirana, Manizales and Natal, we recruited participants through their neighbourhood primary care centres by selecting a random sample of older adults registered at each.[19] The response rate was over 90%.[19] Ethics' committees in Canada prohibited researchers directly contacting potential participants. Invitations to participate in the project were therefore sent indirectly via family physicians.[19] Thirty per cent of people receiving a letter of invitation from their doctor in Kingston and St. Hyacinthe contacted the IMIAS research team; 95% agreed to participate.[19] Comparison with 2006 Canadian census data suggests participants in Kingston were more educated than the general population of that city, while participants from St. Hyacinthe had similar educational levels to inhabitants of that city. Otherwise, characteristics between those recruited and the sampling frame were very similar.[19] At all sites, over 80% of older adults were registered at a health centre or had a primary care physician;[19] it is unlikely that our recruitment strategy systematically excluded a large segment of older adult population.

Exclusion Criterion

Those with four or more errors on the orientation scale of the Leganes Cognitive Test;[20] low scores indicate inability to complete study procedures.

Measurements

Study procedures were carried out at the participant's home, in the local language, by a trained interviewer. Detailed descriptions of data collection procedures are provided elsewhere.[19]

Metabolic syndrome

Except for the measure of insulin resistance, we defined MetS according to the Adult Panel Treatment III (ATP III) criteria.[21] IMIAS did not collect fasting glucose and the corresponding glycosylated haemoglobin (HbA1c) value was used instead.[22] Thus, MetS was defined as the presence of three or more of the following: abdominal obesity measured by waist circumference (women >88cm; men >102cm); elevated triglycerides (≥150mg/dL); low high-density lipoprotein cholesterol (HDL-C men <40mg/dL; HDL-C women <50mg/dL); elevated HbA1c (≥5.7%); and high blood pressure (≥135 mmHg systolic and/or ≥85 mmHg diastolic).

Socioeconomic and demographic characteristics

We categorized education as: less than secondary school and/or illiterate, some secondary school to completed secondary school, and post-secondary education. A participant's living arrangements were determined with the following questions: Do you live alone (Yes/No)? (If no) Who do you live with? Responses were then categorized as: Alone, spouse only, and multiple people.

We determined exposure to childhood social and economic adversity with a scale that varied from zero to three including parental alcohol or drug abuse, witnessing family physical violence, and having been physically abused (childhood social adversity); poor economic status, hunger, and parental unemployment (childhood economic adversity).[23] Occupation was grouped into five categories: non-manual, service, agriculture, manual, and housewife, according to self-reported longest held occupation (based on International Labour Organization categories). We enquired about current annual income levels. Based on the annual minimum salary for each site, individuals were categorized as poor, middle, upper middle, and high income. For example, in Canada, the minimum salary is $19680CAN/year. Thus, we categorized Canadian participants as poor if they earned less than $20000CAN/year. Those who earned more than the minimum salary but less than twice it ($20-39, 999) were classified as middle income, while those that earned twice or higher the minimum salary, but less than three times it, were classified as upper-middle ($40-59,999), and those that earned 3 times or more the minimum salary (≥$60, 000) were classified as upper-income. This was done for each site based on the site-specific minimum salary. Income sufficiency was assessed according: To what extent does your income allow you to meet your needs? Responses were categorized into: Very sufficient, sufficient, and not (at all) sufficient. We asked participants about their work history in the past two weeks and categorized them as: worked with remuneration; worked without remuneration; had a job, but did not work; retired or pensioned; and did not work. We also asked participants if they currently smoke. Responses were categorized as regular, occasional, used to be a smoker, and never. Finally, we assessed minutes of physical activity per week with a validated computer-animated assessment tool.[24]

Statistical analysis

Descriptive statistics summarize overall sample characteristics. Because the distributions were positively skewed for some measures, we report the median, first and third quartiles for all continuous variables. We performed Chi-square tests to investigate the associations between MetS and categorical independent variables and carried out two-sample t-tests to examine mean differences in biomarkers. Random Forest method was used to impute missing physical activities (n=59).[25]

Model-based recursive partitioning method (MOB) was applied to cluster individuals into subgroups with similar response values.[26-28] MOB is reminiscent of the classification and regression tree (CART) algorithms, which split the datasets into subsets based on independent (partitioning) variables, of which the distributions of the response values are most different.[13] Whereas CART trees have constant fits in the terminal nodes, MOB trees have parametric models with one or more predictor variables controlled in each step of the partitioning, and in their terminal nodes. For instance, age is controlled in the MOB analysis of MetS using logistic regression models and the MOB algorithm cycles iteratively through the following steps: (1) fit the logistic regression with MetS as response variable and age as control variable, (2) test for parameter instability over a set of partitioning variables (socioeconomic and demographic characteristics) while controlling for age, (3) if there is some overall parameter instability, split the data set with respect to the variable associated with the highest instability (i.e. the smallest p-value), (4) repeat the procedure in each of the resulting subsamples with different risk of MetS. The process is termed recursive because each sub-population may be split a number of times until a particular stopping criterion is reached. Our stopping criteria were: 5% level of significance and minimum sample size of 100 at terminal nodes. For continuous partitioning variables, MOB tests and selects an optimal cut-off point and split subjects into two subgroups.[26-28]

We performed MOB for MetS, systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, log transformed triglyceride, HDL-C, and HbA1c, controlling for age. The partitioning variables included social and behavioural risk characteristics described previously. Statistical software R (version 3.2.2) and the R package "party" were used.

Ethics

Institutional review for this project was obtained from the relevant organizations at each site: the Institute of Public Health in Albania, the Federal University of Rio Grande do Norte in Brazil, the

University of Caldas in Colombia, the University of Montreal Hospital Research Centre (CR-CHUM) and Queen's University in Canada. Written informed consent was obtained from all participants.

RESULTS

Complete data on all variables were available for 1628 (81%) participants. Table 1 presents the frequency of MetS according to the participant characteristics. MetS was observed in 43% participants, 50% of women and 35% of men. For most variables, there were important differences in the proportion of participants with MetS. It concentrated among those of lower socioeconomic status: those with lower education, lower incomes, manual workers and housewives. More MetS was observed among those reporting childhood adversities. Those with MetS reported had higher mean blood pressure, waist circumference, HbA1c, triglyceride, low HDL measures, and walked less on average than those without it.

---Insert table 1 here (see next page)---

Table 1: Descriptive characteristics of the participants and frequency of metabolic syndrome.

	Overall (N=1628)	Metabolic Syndrome Yes (42.7%)	No (57.3%)	*p-value**
	N (%)	N (%)	N (%)	
Site				
Kingston	289(17.8%)	92(31.8%)	197(68.2%)	<.0001
St. Hyacinthe	310(19.0%)	96(31.0%)	214(69.0%)	
Tirana	344(21.1%)	171(49.7%)	173(50.3%)	
Manizales	374(23.0%)	172(46.0%)	202(54.0%)	
Natal	311(19.1%)	164(52.7%)	147(47.3%)	
Sex				
Female	844(51.8%)	424(50.2%)	420(49.8%)	<.0001
Male	784(48.2%)	271(34.6%)	513(65.4%)	
Educational Attainment				
Primary / illiterate	760(46.7%)	366(48.2%)	394(51.8%)	0.0001
Secondary	217(13.3%)	91(41.9%)	126(58.1%)	
Post-secondary	651(40.0%)	238(36.6%)	413(63.4%)	
Current Living Arrangements				
Alone	254(15.6%)	100(39.4%)	154(60.6%)	0.0001
Spouse only	609(37.4%)	225(36.9%)	384(63.1%)	
Other	765(47.0%)	370(48.4%)	395(51.6%)	
Adult Occupation				
Non manual	593(36.4%)	211(35.6%)	382(64.4%)	<.0001
Service	160(9.8%)	67(41.9%)	93(58.1%)	
Agriculture	94(5.8%)	41(43.6%)	53(56.4%)	
Manual	607(37.3%)	274(45.1%)	333(54.9%)	
Housewife	174(10.7%)	102(58.6%)	72(41.4%)	
Current Income				
Poor	417(25.6%)	189(45.3%)	228(54.7%)	0.001
Middle	704(43.2%)	315(44.7%)	389(55.3%)	
Upper middle	346(21.3%)	145(41.9%)	201(58.1%)	
High	161(9.9%)	46(28.6%)	115(71.4%)	
Perceived Income Sufficiency				
Very sufficient	339(20.8%)	102(30.1%)	237(69.9%)	<.0001
Sufficient	537(33.0%)	215(40.0%)	322(60.0%)	
Not (at all) sufficient	752(46.2%)	378(50.3%)	374(49.7%)	
Childhood Economic Adversity				
No adversities	858(52.7%)	351(40.9%)	507(59.1%)	0.0291
One adversity event	453(27.8%)	186(41.1%)	267(58.9%)	
Two adversity events	212(13.0%)	102(48.1%)	110(51.9%)	
Three adversity events	105(6.4%)	56(53.3%)	49(46.7%)	
Childhood Social Adversity				
No adversities	1, 231(75.6%)	505(41.0%)	726(59.0%)	0.0792
One adversity event	245(15.0%)	113(46.1%)	132(53.9%)	
Two adversity events	119(7.3%)	59(49.6%)	60(50.4%)	
Three adversity events	33(2.0%)	18(54.5%)	15(45.5%)	

Table 1 (continued): Descriptive characteristics of the participants.

	Overall (N=1628)	Metabolic Syndrome Yes (42.7%)	Metabolic Syndrome No (57.3%)	*p-value**
	N (%)	N (%)	N (%)	
Smoker				
Regular	138(8.5%)	64(46.4%)	74(53.6%)	0.109
Occasional	37(2.3%)	18(48.6%)	19(51.4%)	
Used to be	676(41.5%)	265(39.2%)	411(60.8%)	
Never	777(47.7%)	348(44.8%)	429(55.2%)	
Current Employment Status				
Worked with remuneration	185(11.4%)	66(35.7%)	119(64.3%)	0.011
Worked w/o remuneration	201(12.3%)	105(52.2%)	96(47.8%)	
Had a job, but did not work	25(1.5%)	9(36.0%)	16(64.0%)	
Retired or Pensioned	1, 119(68.7%)	468(41.8%)	651(58.2%)	
Did not work	98(6.0%)	47(48.0%)	51(52.0%)	
	Median(Q1, Q3)	Median(Q1, Q3)	Median(Q1, Q3)	
Age (year)	69(67, 72)	69 (67, 72)	69 (67, 71)	0.0451
Physical Activity (minutes/week)	20(9, 39)	15 (6, 32)	24(10, 43)	<.0001
SBP (mmHg)	138(126, 152)	143(134, 157)	132(122, 146)	<.0001
DBP (mmHg)	79 (71, 86)	81(74, 88)	77(70, 84)	<.0001
Waist (cm)	96(88, 104)	101(94, 108)	92(85, 100)	<.0001
HbA1c (%)	5.8(5.5, 6.2)	6.1(5.8, 6.6)	5.7(5.4, 6.0)	<.0001
Triglyceride (mg/dL)	126(91, 172)	165(125, 211)	105 (78, 134)	<.0001
HDL (mg/dL)	50(43, 60)	45(39, 53)	55(47, 63)	<.0001

**p-values:* obtained from Chi-square tests of association between MetS (Yes/No) and categorical explanatory variables, and t-tests for difference in MetS (Yes/No) for continuous variable

Table 2 presents participant characteristics by study site and shows a notably higher frequency of MetS among participants from the middle-income sites (46-53%) compared to those from the Canadian sties (≈30%).

---Insert table 2 here (see next page)---

Table 2: Descriptive characteristics of the participants by study site.

	Kingston	St. Hyacinthe	Tirana	Manizales	Natal
	289(17.8%)	310(19%)	344(21.1%)	374(23%)	311(19.1%)
	N (%)	N (%)	N (%)	N (%)	N (%)
Metabolic Syndrome					
Yes	92(31.8%)	96(31.0%)	171(49.7%)	172(46.0%)	164(52.7%)
No	197(68.2%)	214(69.0%)	173(50.3%)	202(54.0%)	147(47.3%)
Sex					
Female	152(52.6%)	166(53.5%)	178(51.7%)	190(50.8%)	158(50.8%)
Male	137(47.4%)	144(46.5%)	166(48.3%)	184(49.2%)	153(49.2%)
Educational Attainment					
Primary / illiterate	29(10.0%)	85(27.4%)	54(15.7%)	310(82.9%)	282(90.7%)
Secondary	37(12.8%)	67(21.6%)	79(23.0%)	19(5.1%)	15(4.8%)
Post-secondary	223(77.2%)	158(51.0%)	211(61.3%)	45(12.0%)	14(4.5%)
Current Living Arrangements					
Alone	88(30.4%)	72(23.2%)	31(9.0%)	47(12.6%)	16(5.1%)
Spouse only	127(43.9%)	201(64.8%)	151(43.9%)	68(18.2%)	62(19.9%)
Other	74(25.6%)	37(11.9%)	162(47.1%)	259(69.3%)	233(74.9%)
Adult Occupation					
Non manual	226(78.2%)	158(51.0%)	116(33.7%)	63(16.8%)	30(9.6%)
Service	24(8.3%)	40(12.9%)	23(6.7%)	22(5.9%)	51(16.4%)
Agriculture	2(0.7%)	18(5.8%)	5(1.5%)	37(9.9%)	32(10.3%)
Manual	27(9.3%)	78(25.2%)	199(57.8%)	161(43.0%)	142(45.7%)
Housewife	10(3.5%)	16(5.2%)	1(0.3%)	91(24.3%)	56(18.0%)
Current Income					
Poor	51(17.6%)	109(35.2%)	36(10.5%)	191(51.1%)	30(9.6%)
Middle	97(33.6%)	122(39.4%)	204(59.3%)	112(29.9%)	169(54.3%)
Upper middle	61(21.1%)	62(20.0%)	82(23.8%)	50(13.4%)	91(29.3%)
High	80(27.7%)	17(5.5%)	22(6.4%)	21(5.6%)	21(6.8%)
Perceived Income Sufficiency					
Very sufficient	174(60.2%)	132(42.6%)	5(1.5%)	19(5.1%)	9(2.9%)
Sufficient	101(34.9%)	157(50.6%)	121(35.2%)	89(23.8%)	69(22.2%)
Not (at all) sufficient	14(4.8%)	21(6.8%)	218(63.4%)	266(71.1%)	233(74.9%)
Childhood Economic Adversity					
No adversities	190(65.7%)	201(64.8%)	147(42.7%)	216(57.8%)	104(33.4%)
One adversity event	73(25.3%)	92(29.7%)	89(25.9%)	108(28.9%)	91(29.3%)
Two adversity events	24(8.3%)	15(4.8%)	75(21.8%)	28(7.5%)	70(22.5%)
Three adversity events	2(0.7%)	2(0.6%)	33(9.6%)	22(5.9%)	46(14.8%)
Childhood Social Adversity					
No adversities	210(72.7%)	229(73.9%)	281(81.7%)	287(76.7%)	224(72.0%)
One adversity event	42(14.5%)	54(17.4%)	27(7.8%)	63(16.8%)	59(19.0%)
Two adversity events	25(8.7%)	22(7.1%)	30(8.7%)	18(4.8%)	24(7.7%)
Three adversity events	12(4.2%)	5(1.6%)	6(1.7%)	6(1.6%)	4(1.3%)

Table 2 (continued): Descriptive characteristics of the participants by study site.

	Kingston	St. Hyacinthe	Tirana	Manizales	Natal
	289(17.8%)	310(19%)	344(21.1%)	374(23%)	311(19.1%)
Smoker					
Regular	14(4.8%)	19(6.1%)	43(12.5%)	37(9.9%)	25(8.0%)
Occasional	3(1.0%)	5(1.6%)	12(3.5%)	13(3.5%)	4(1.3%)
Used to be	141(48.8%)	169(54.5%)	81(23.5%)	147(39.3%)	138(44.4%)
Never	131(45.3%)	117(37.7%)	208(60.5%)	177(47.3%)	144(46.3%)
Current Employment Status					
Worked with remuneration	43(14.9%)	39(12.6%)	8(2.3%)	58(15.5%)	37(11.9%)
Worked w/o remuneration	8(2.8%)	18(5.8%)	8(2.3%)	99(26.5%)	68(21.9%)
Had a job, but did not work	8(2.8%)	2(0.6%)	4(1.2%)	8(2.1%)	3(1.0%)
Retired or Pensioned	228(78.9%)	246(79.4%)	323(93.9%)	133(35.6%)	189(60.8%)
Did not work	2(0.7%)	5(1.6%)	1(0.3%)	76(20.3%)	14(4.5%)
	Median(Q1,Q3)	Median (Q1,Q3)	Median(Q1,Q3)	Median(Q1,Q3)	Median(Q1,Q3)
Age (year)	69(67, 71)	68(67, 71)	70(66, 72)	69(67, 72)	69(67, 71)
Physical Activity (minutes/wk)	26(9, 51)	24(9, 39)	27(11, 48)	17(9, 39)	10(4, 23)
SBP (mmHg)	135(124, 145)	134(125, 143)	144(130, 161)	133(123, 146)	146(130, 161)
DBP (mmHg)	77(71, 83)	75(68, 81)	84(75, 91)	79(72, 86)	78(71, 86)
Waist (cm)	96(88, 107)	94(87, 102)	102(95, 107)	90(83, 96)	100(93, 106)
HbA1c (%)	5.8(5.5, 6.0)	5.8(5.5, 6.1)	5.6(5.3, 6.3)	5.9(5.7, 6.2)	6.0(5.6, 6.5)
Triglyceride (mg/dL)	88(60, 136)	122(91, 159)	130(106, 165)	140(106, 201)	131(97, 187)
HDL (mg/dL)	54(45, 66)	56(46, 67)	47(41, 52)	48(39, 57)	52(47, 61)

Figure 1 depicts the MOB tree for MetS, adjusting for participant age. The highest estimates of MetS prevalence were observed in clusters of women from the middle-income study sites (Tirana, Manizales, Natal). In these clusters, the predicted proportion with MetS varied from 58 to 68%, depending on education. Better-educated women from these sites had more MetS. Among women from the Canadian sites, less walking time per week distinguished the higher from lower probability cluster. The lowest predicted proportion (26%) of MetS was observed in men with post-secondary education reporting no childhood social adversities, and in women from the

Canadian sites who had more walking time per week. The graphs under each node in figure 1 depict the estimated prevalence according to age and demonstrate that for certain nodes (e.g. 7), there is a strong association between increasing age and higher estimated MetS prevalence.

---Insert Figure 1 here---

The supplementary files contain the MOB trees for MetS components. Each tree depicts unique clusters that do not correspond with those observed for MetS as a whole. For example, the highest estimated mean systolic blood pressure (154 mmHg) was observed among participants from Tirana and Natal, with income insufficiency, and who smoked regularly or used to. For this outcome, in contrast to MetS as a whole, sex was not a partitioning variable. Overall, in all models except HDL, study site was the primary partitioning variable and in some cases (triglycerides), the only one. Typically, participants from Natal and Tirana had unfavourable estimates for MetS components; however, participants from Manizales had the highest estimated triglyceride concentrations (145 mg/dL). Participant sex was a key partitioning variable for DBP, waist circumference, and HDL concentration. Other partitioning variables for one or two of the MetS components included: weekly walking time, current employment status, perceived income sufficiency, living arrangements, smoking, adult occupation, and current income.

DISCUSSION

The MOB technique identified distinct clusters of individuals with differential probabilities of MetS and its components, according to multiple social and behavioural risk factors. For the syndrome as a whole, in clusters of women from middle-income sites, the predicted proportion with MetS was quite high (58 or 68% depending on the cluster). In clusters of men, the predicted proportion with MetS was lower (26, 38 or 41% depending on the cluster) and highest among men reporting childhood social adversities (41%). MetS in women from the Canadian sites varied considerably based on average walking time per week. Women from Kingston and St. Hyacinthe who walked minimally (>11 min/week) had predicted probabilities of MetS identical to men with post-secondary education and no childhood social adversities. This work demonstrates the potential of using MOB to identify joint effects in a moderately-sized sample of individuals. It raises questions for future investigation, especially related to the concentration of risk(s) in certain subgroups.

This study corroborates previous findings that the prevalence of MetS varies according to age, sex, and socioeconomic status.[4, 10, 29] Consistent with other studies, overall, we observed a concentration of MetS in participants of lower socioeconomic status[10, 30, 31]; although, among women from the middle-income sites, MetS was more prevalent among those with post-secondary education. Better educated women from the middle-income sites likely had/have more money to afford obesogenic, Westernized foods and over their lifetimes, may have engaged in less exercise, as educational attainment may have allowed them to “escape” physically strenuous jobs. Consistent with other research[32], early life adversity was associated to higher prevalence estimates of MetS; however, this association was only observed in men, whereas it has been observed in both men and women elsewhere[32]. The strong context-specificity of our findings highlights the utility of using MOB to identify unique admixtures that might have been overlooked with traditional statistical techniques and/or would have been impossible to identify without a very large sample size.

When applying MOB, we observed distinct risk clusters according to study site and participant sex, education and childhood adversity. These findings support a dynamic interplay between contextual and social risk factors and the concentration of risks in certain subgroups, which is consistent with the notion of vulnerable populations proposed by Frohlich and Potvin.[3] Accordingly, vulnerable populations are defined by shared social characteristics that put them at "higher risk of risks".[3 pp218] These risks and their accumulation across the life-course relate to fundamental causes linked to one's social position within the predominant social structure.[3] This may explain why study site and sex were key partitioning variables. Study site proxies societal opportunities for education, occupation, and income and expectations surrounding behaviours and diet. The clustering by site supports research underscoring the importance of context in patterning the risk exposures of individuals.[3, 33] Sex/gender likely underpins access to resources such as money, knowledge and power affecting health outcomes through multiple risk factors.[34]

In studies with large sample sizes (>10, 000 participants), complex joint-effects have been observed with traditional regression analysis techniques. For example, using data from representative samples of United States' adults aged 25 and older, Loucks *et al.* reported that overall, the prevalence of MetS was similar in women and men, both low education and poverty were associated with MetS, and the social gradient of the prevalence of MetS was more pronounced in women than in men.[11] These United States' findings differ from ours since in IMIAS, sex was the first stratifying variable, with an overall higher frequency of MetS in women than in men. However, for both men and women in our study, education was an important predictor of MetS at most sites; although, the direction of the association between education and

MetS was not consistent. Among women from the middle-income sites, greater educational attainment was associated with a higher predicted prevalence of MetS. Among men with no childhood social adversity, low educational attainment was associated to a higher predicted prevalence of MetS. In the study by Loucks et al., education was generally not associated to MetS in men; although, their study did not consider childhood adversity experiences[10, 11], in contrast to our own work. Interestingly, in the Loucks et al. study, among men, low education was associated with the MetS components of abdominal obesity, hypertension, and hyperglycemia [11].

When MOB was applied to the syndrome components, only study site and participant sex were consistent partitioning variables for most components. In general, when measures of socioeconomic status were partitioning variables, lower status was associated with poorer outcomes. For example, income insufficiency predicted higher mean diastolic blood pressure among Tirana participants. Measures of socioeconomic status appeared as partitioning variables more frequently than risk behaviours. This is consistent with recent work analysing individual-level data from more than 1.7 million people in which low socioeconomic status was associated with premature mortality across multiple disease categories and ranked 3rd in population attributable fraction for mortality among a large list of risk factors (physical inactivity ranked 2nd). [35] In our study, higher mean weekly physical activity predicted lower waist circumferences and higher HDL concentrations, consistent with the literature.[36-38]

This study has strengths. First is the use of the MOB technique. Traditional CART methods have the vulnerability of over-fitting, selection bias and no concept of statistical significance. Thus pruning and cross-validation methods are used to avoid the over-fitting problems characteristic of

CART. MOB is implemented via hypothesis tests, which leads to regression models whose predictive performance is equivalent to optimally pruned trees, therefore offering an intuitive and computationally efficient solution to the over-fitting problem, and the resulting models are easier to communicate to practitioners.[27, 39] Finally, this is one of the very few studies that apply MOB to examine social and behavioural risk clusters for disease. Most research applying recursive partitioning focuses on identifying patient subgroups within a clinical setting [26] and/or how to better define components that constitute syndromes such as MetS [40].

This study has limitations. Study site and sex are structuring variables that may mask more proximal risk factors for disease. Individual risk behaviours, such as smoking, may be ubiquitous within certain subgroups,[33] rendering it difficult to detect the influence of these behaviours on MetS using the MOB technique. Another limitation is that we used a single waist circumference cut-off value for all populations. Arguments exist for country and/or ethnicity-specific waist circumference cut-offs, but more work is required to optimally determine these.[41] Finally, we did not collect individual dietary data or data on the early nutritional environment.[32]

Conclusion

We applied a recursive partitioning technique to investigate risk clustering for MetS in an international, multi-site study of community-dwelling older adults and observed unique risk clusters according to mostly contextual and socioeconomic characteristics. The main partitioning variables in our results were study site and sex, which for most people are not easily modifiable. However, the policies and opportunities afforded to residents of different communities and to men versus women can be modified and do vary dramatically on a global scale, which likely helps to explain the large variations in MetS prevalence across communities and even the inconsistencies observed across the literature in which women sometimes, but not always, have higher MetS prevalence. By identifying risk clusters with techniques such as MOB, we can generate novel hypotheses about both contributing and protective factors that might have been missed with traditional regression techniques, as relatively few studies have sufficient resources to recruit large enough samples for multiple order joint effects. MOB may also prove particularly informative in studies with much larger samples, such as the Health and Retirement Study, where it can be used generate new hypotheses about risk clustering and then more traditional deterministic techniques can be applied to the same sample in order to corroborate or contradict these hypotheses. Finally, with regards to both clinical practice and health promotion activities, identifying risk clusters is important for targeting purposes, as the intensity and type of programs may differ according to sub-groups.[15]

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CONTRIBUTION STATEMENT

CMP and MVZ conceived of the study. CMP and YW analysed and interpreted the data. CMP, YW, JFG, and MVZ contributed to the writing and editing of this manuscript.

DATA SHARING

Extra data is available through registration on the IMIAS website (http://www.imias.ufrn.br). Registered users can request IMIAS data through a data request form.

FUNDING

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COMPETING INTERESTS

None declared

PATIENT CONSENT

Written informed consent was obtained from all IMIAS participants.

FIGURE 1

Model based recursive partitioning for metabolic syndrome controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean proportions of metabolic syndrome obtained from logistic regression models by age. The predicted mean proportion of metabolic syndrome and 95% confidence interval for each terminal node are listed under the plots.

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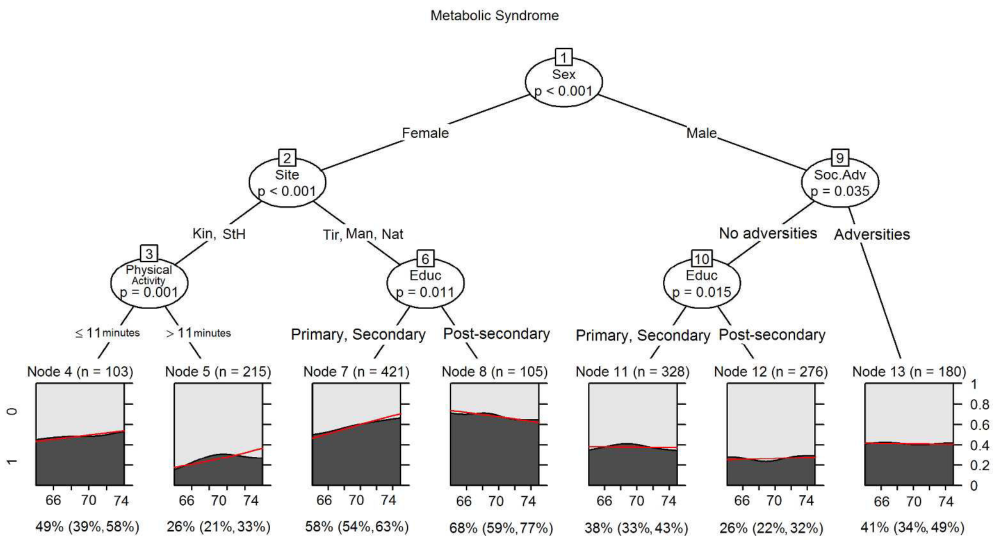
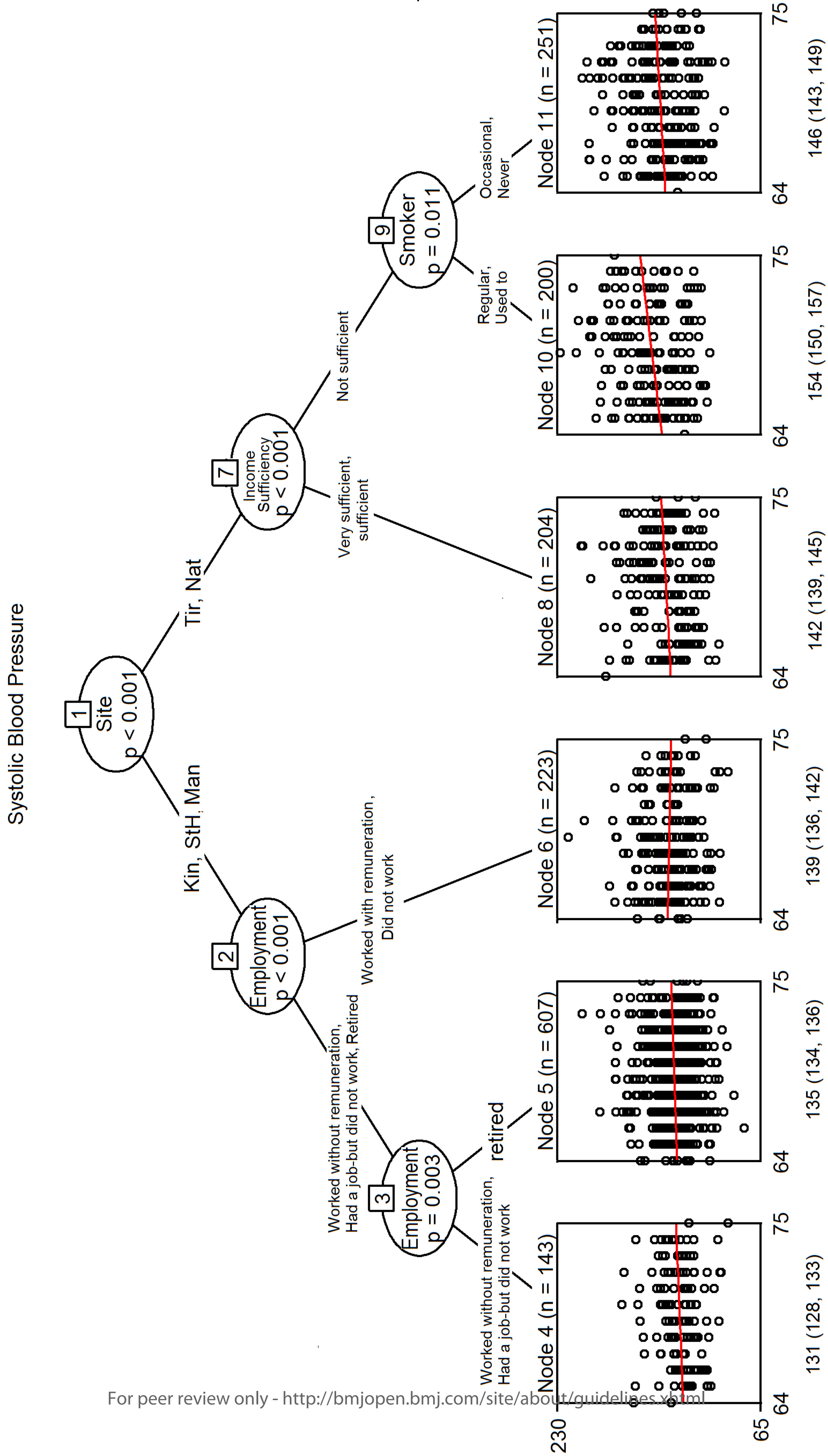
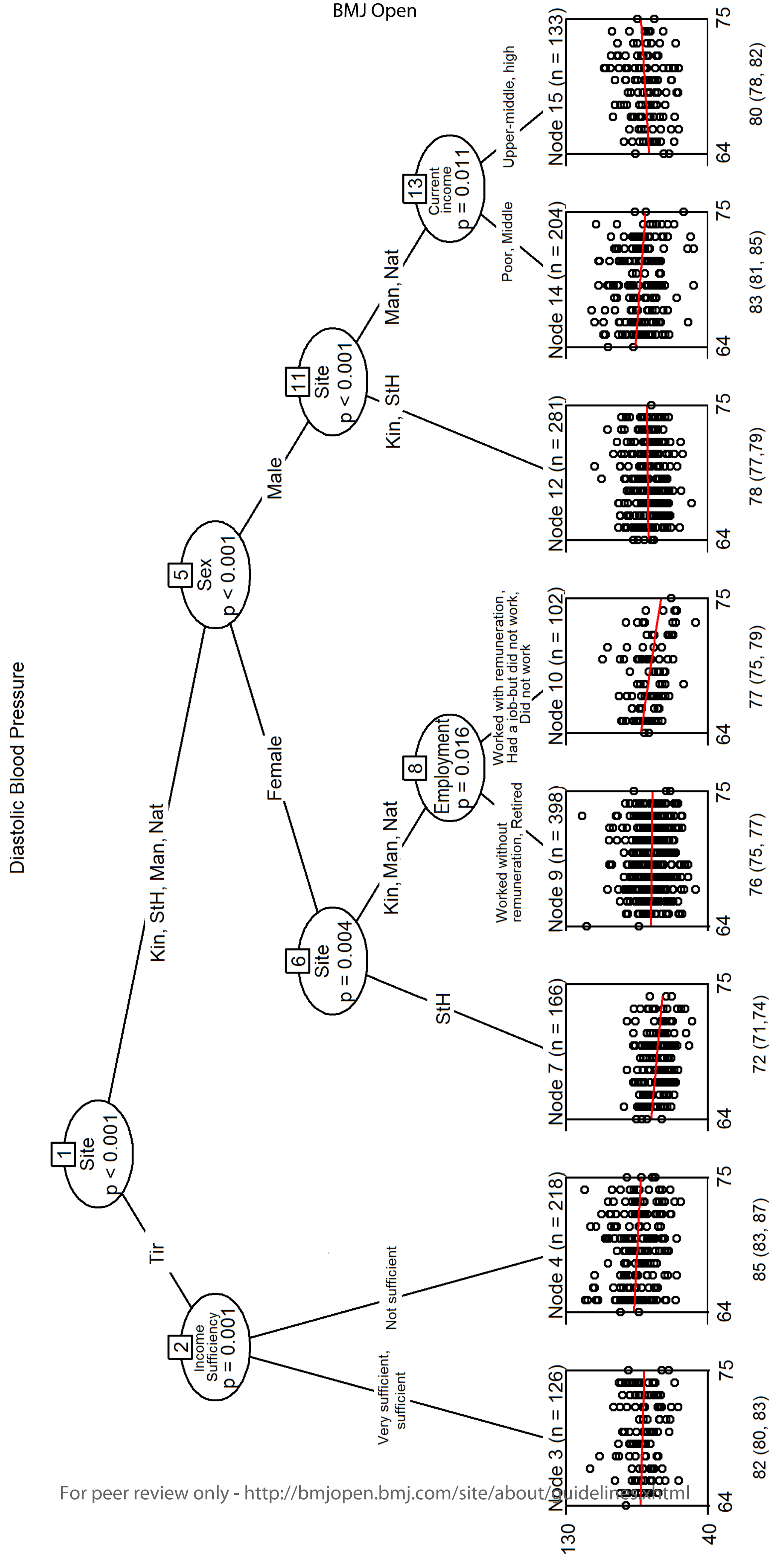
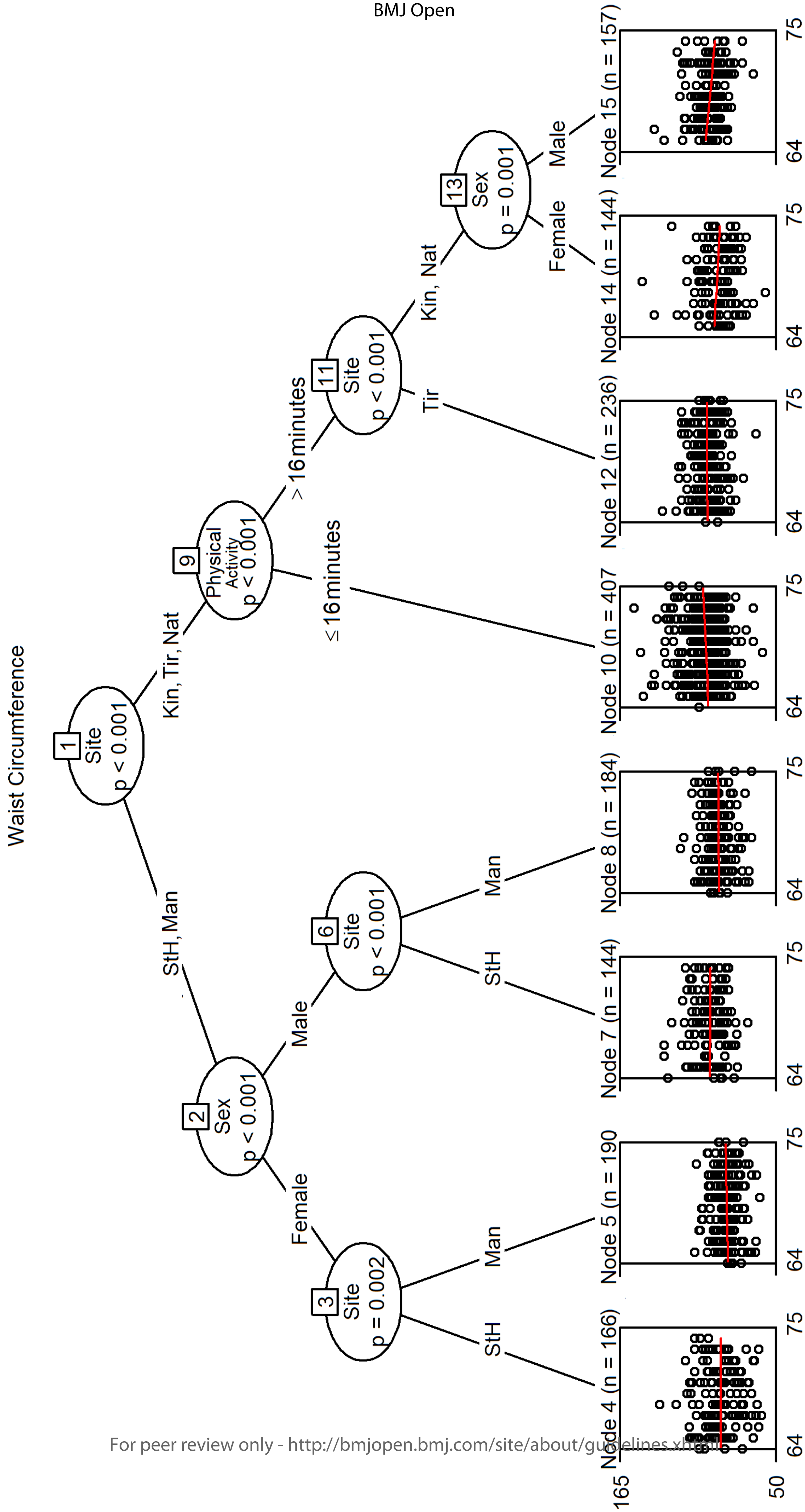


Model based recursive partitioning for metabolic syndrome controlling for age. The horizontal axis of the terminal plots is age (64-75y), and the vertical axis shows the predicted mean proportions of metabolic syndrome obtained from logistic regression models by age. The predicted mean proportion of metabolic syndrome and 95% confidence interval for each terminal node are listed under the plots.

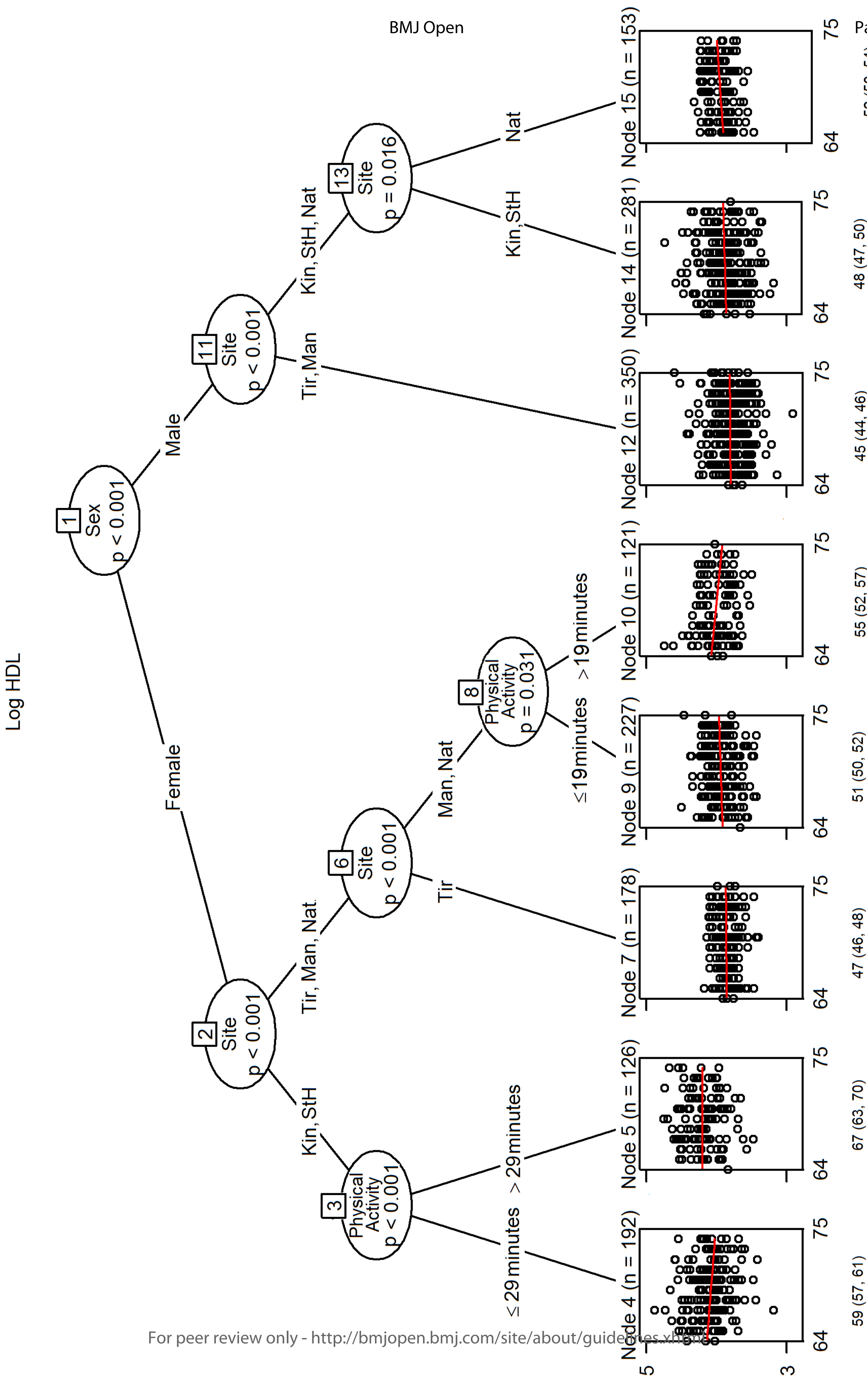
329x188mm (216 x 216 DPI)

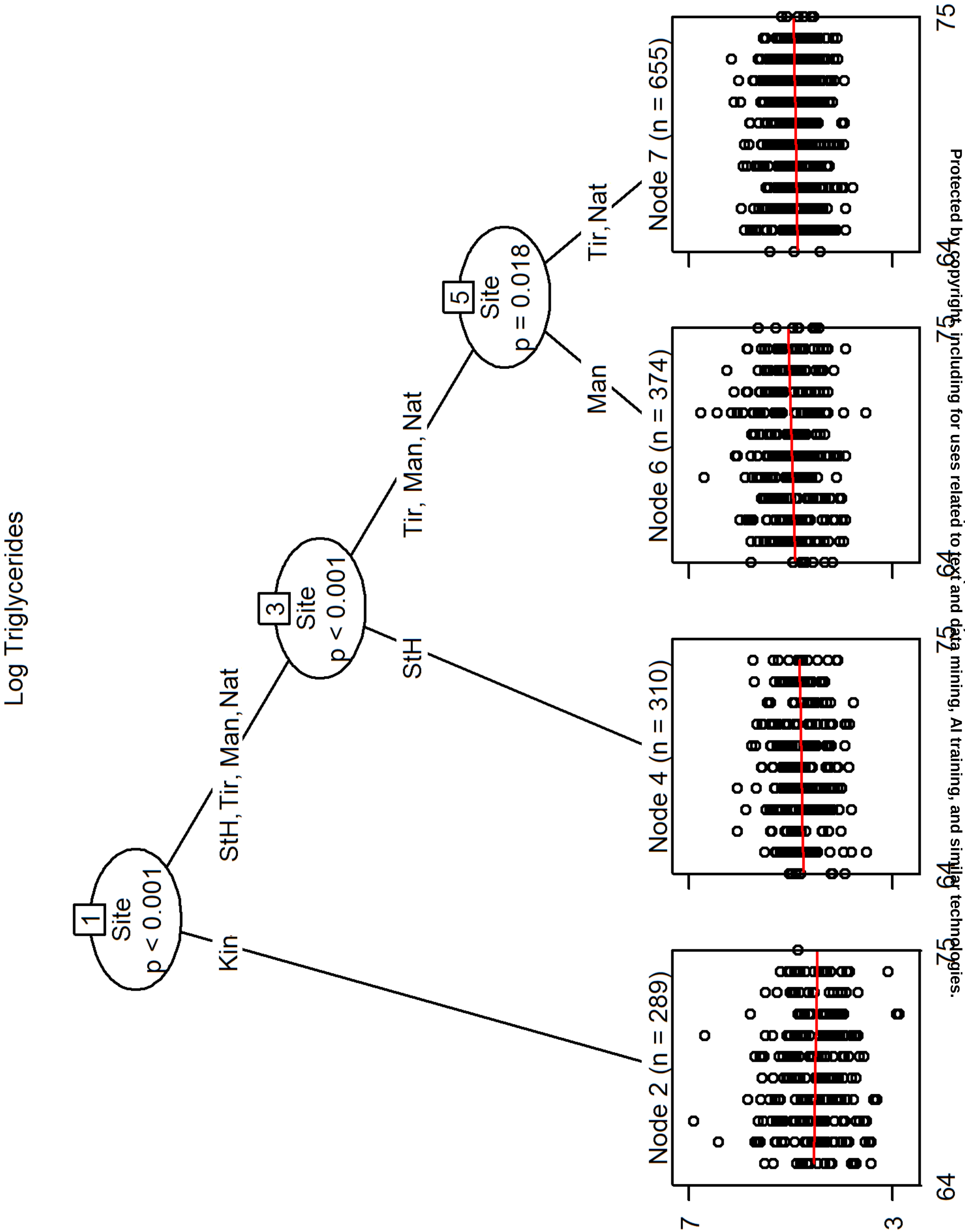

Systolic Blood Pressure
1
Site
p < 0.001
Tir, Nat
Kin, StH, Man
7
Income
Sufficiency
p < 0.001
Not sufficient
Very sufficient,
sufficient
9
Smoker
p = 0.011
Regular,
Used to
Occasional,
Never
2
Employment
p < 0.001
Worked with remuneration,
Did not work
Worked without remuneration,
Had a job-but did not work, Retired
3
Employment
p = 0.003
retired
Worked without remuneration,
Had a job-but did not work
Node 4 (n = 143)
131 (128, 133)
Node 5 (n = 607)
135 (134, 136)
Node 6 (n = 223)
139 (136, 142)
Node 8 (n = 204)
142 (139, 145)
Node 10 (n = 200)
154 (150, 157)
Node 11 (n = 251)
146 (143, 149)
64
75
230
65

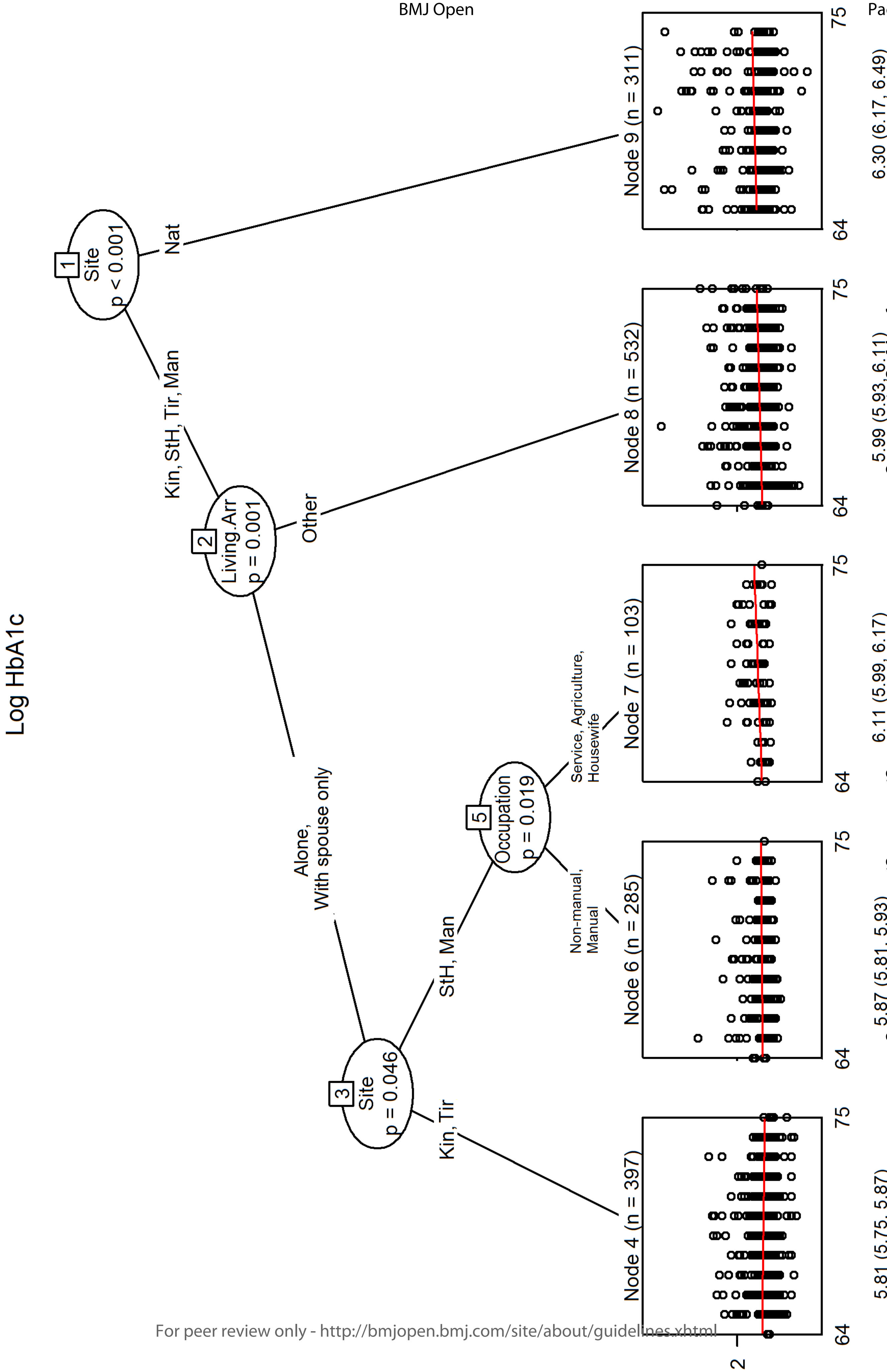

Diastolic Blood Pressure
1 Site p < 0.001
Tir
Kin, StH, Man, Nat
2 Income Sufficiency p = 0.001
Very sufficient, sufficient
Not sufficient
5 Sex p < 0.001
Male
Female
6 Site p = 0.004
StH
Kin, Man, Nat
8 Employment p = 0.016
Worked without remuneration, Retired
Worked with remuneration, Had a job-but did not work, Did not work
11 Site p < 0.001
Kin, StH
Man, Nat
13 Current income p = 0.011
Poor, Middle
Upper-middle, high
Node 3 (n = 126)
Node 4 (n = 218)
Node 7 (n = 166)
Node 9 (n = 398)
Node 10 (n = 102)
Node 12 (n = 281)
Node 14 (n = 204)
Node 15 (n = 133)
130
40
64
75
82 (80, 83)
85 (83, 87)
72 (71,74)
76 (75, 77)
77 (75, 79)
78 (77,79)
83 (81, 85)
80 (78, 82)



Waist Circumference
1
Site
p < 0.001
Kin, Tir, Nat
StH, Man
9
Physical Activity
p < 0.001
> 16 minutes
≤ 16 minutes
11
Site
p < 0.001
Kin, Nat
Tir
13
Sex
p = 0.001
Female
Male
2
Sex
p < 0.001
Male
Female
6
Site
p < 0.001
StH
Man
3
Site
p = 0.002
StH
Man
Node 15 (n = 157)
Node 14 (n = 144)
Node 12 (n = 236)
Node 10 (n = 407)
Node 8 (n = 184)
Node 7 (n = 144)
Node 5 (n = 190)
Node 4 (n = 166)
165
50
64
75
99 (97 , 100)
94 (92, 96)
101 (100, 102)
102 (101, 103)
92 (91, 94)
99 (97 , 100)
86 (85, 88)
91 (89, 92)


Log HDL
1
Sex
p < 0.001
Male
Female
11
Site
p < 0.001
Kin, StH, Nat
Tir, Man
13
Site
p = 0.016
Nat
Kin, StH
2
Site
p < 0.001
Tir, Man, Nat
Kin, StH
6
Site
p < 0.001
Man, Nat
Tir
8
Physical Activity
p = 0.031
≤ 19minutes
> 19minutes
3
Physical Activity
p < 0.001
≤ 29minutes
> 29minutes
Node 15 (n = 153)
Node 14 (n = 281)
Node 12 (n = 350)
Node 10 (n = 121)
Node 9 (n = 227)
Node 7 (n = 178)
Node 5 (n = 126)
Node 4 (n = 192)
52 (50, 54)
48 (47, 50)
45 (44, 46)
55 (52, 57)
51 (50, 52)
47 (46, 48)
67 (63, 70)
59 (57, 61)
64
75
5
3


Log Triglycerides
1
Site
p < 0.001
Kin
StH, Tir, Man, Nat
3
Site
p < 0.001
StH
Tir, Man, Nat
5
Site
p = 0.018
Man
Tir, Nat
Node 2 (n = 289)
Node 4 (n = 310)
Node 6 (n = 374)
Node 7 (n = 655)
7
3
64
75


Log HbA1c
1
Site
p < 0.001
Nat
Kin, StH, Tir, Man
2
Living.Arr
p = 0.001
Other
Alone,
With spouse only
3
Site
p = 0.046
StH, Man
Kin, Tir
5
Occupation
p = 0.019
Service, Agriculture,
Housewife
Non-manual,
Manual
Node 4 (n = 397)
Node 6 (n = 285)
Node 7 (n = 103)
Node 8 (n = 532)
Node 9 (n = 311)
64
75
2
5.81 (5.75, 5.87)
5.87 (5.81, 5.93)
6.11 (5.99, 6.17)
5.99 (5.93, 6.11)
6.30 (6.17, 6.49)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Page No	Recommendation
Title and abstract	1 2	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4-5	Explain the scientific background and rationale for the investigation being reported
Objectives	6	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6	Present key elements of study design early in the paper
Setting	6-7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	7	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7-9	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	7-9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	7-9	Describe any efforts to address potential sources of bias
Study size	6	Explain how the study size was arrived at *(in separate publication)*
Quantitative variables	7-9 +Analysis	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	9-10	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	n/a	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	Tables 1 & 2	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	Tables & Figures	Report numbers of outcome events or summary measures
Main results	Tables and Figures	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear

		which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	16 & suppl. files	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	16-17	Summarise key results with reference to study objectives
Limitations	Limitations box and 20	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	Whole discussion	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	Conclusion	Discuss the generalisability (external validity) of the study results
Other information		
Funding	Funding	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based