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To cite this article: Adetola Koleade, Dr. Jamie Farrell, Dr. Gerald Mugford & Dr. Zhiwei Gao (2019): Female-specific risk factors associated with risk of ACO (Asthma COPD Overlap) in Aboriginal People, Journal of Asthma, DOI: [10.1080/02770903.2019.1621890](https://doi.org/10.1080/02770903.2019.1621890)

To link to this article: <https://doi.org/10.1080/02770903.2019.1621890>



Accepted author version posted online: 20 May 2019.



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TITLE: Female-specific risk factors associated with risk of ACO (Asthma COPD Overlap) in Aboriginal People

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Abstract

Objective: Sex differences in incidence, susceptibility and severity of many chronic respiratory diseases have been long recognized. Asthma-COPD Overlap (ACO) is newly recognised disease with its management guidelines reported in 2015. The objective of this analysis is to identify the female-specific risk factors associated with ACO in Aboriginal people.

Methods: The Aboriginal Peoples Survey 2012 (N=28,410) is the fourth cycle of a national cross-sectional survey representative of the First Nations living off reserve, Metis and Inuit. The 2012 APS collected information on employment, education, health status, housing, family background and income. Survey Logistic Regression was used to identify the significant risk factors for ACO in the multivariate analysis.

Results: The prevalence of ACO was 1.65% and 3.53% in males and females respectively. The following factors were significantly associated with increased risk of ACO in both males and females: increased age, living in Quebec, longer hours of work per week, living in a rented dwelling and dwelling in need of major repairs. However, three factors including marital status (being widowed, separated or divorced), smoking status (being a current daily smoker) and having a diagnosis of diabetes were significantly associated with increased risk of ACO in females not males.

Conclusion: The results of our study may offer useful evidence for future development of female-specific prevention and public health intervention programs in aboriginal communities to reduce the burden of ACO.

Keywords: aboriginal, Asthma-COPD Overlap (ACO), Canada, gender differences, respiratory diseases

Introduction

Asthma-COPD Overlap (ACO), is a newly recognised disease with its management guidelines reported in 2015.¹ As explained in our previous paper and other studies²⁻⁴, ACO is a disease that shares the clinical features of asthma and COPD. It is poorly characterized in terms of genetic risk factors, clinical features, treatment response and prognosis which makes it difficult to diagnose.^{5,6} Patients with ACO had a significantly higher prevalence of comorbidities, greater health care utilization rates and nearly doubled health care costs.^{7,8} Aboriginal people are at a higher risk of many chronic respiratory diseases.^{9,10} Our recent study showed that female aboriginal people were approximately two times more likely to have ACO than male aboriginal people.² However, female specific factors associated with ACO in Aboriginal people is still unknown.

Sex and Gender differences in incidence, susceptibility and severity of many chronic respiratory diseases have been long recognized.^{11,12} Females generally experience more severe symptoms and a worse prognosis for asthma compared to males of the same age;¹¹ while historically, males are at higher risk for COPD than females.¹² Although the biological mechanisms of sex differences are not fully understood, recent evidence suggests the involvement of sex-related hormones. Epidemiological studies consistently show differences in many lung diseases before and after both puberty and menopause when sex hormones experience dramatic changes.¹³⁻¹⁵

In addition to sex hormones, many epidemiological studies also report environmental and lifestyle risk factors for chronic respiratory diseases, such as COPD. Females in rural areas exposed to high levels of biomass smoke and other indoor air pollutants due to routine cooking are associated with higher levels of respiratory diseases compared to males, and about 50% of deaths in females were associated with COPD.¹⁶ Another study reported that due to the recent increased rate of cigarette smoking among women, they may be more disposed to the development of severe COPD.¹⁷ In this study, we postulate that many risk factors may be associated with the risk of ACO in female Aboriginal peoples only and not in males using data from the 2012 Aboriginal Peoples Survey (APS).

Methods

Study design:

The 2012 Aboriginal Peoples Survey (APS) was described in detailed in our previous paper.² Briefly, the 2012 APS was a nation-wide survey representative of First Nations living off reserve, Metis and Inuit in Canada. It was collected by Statistics Canada from February to July 2012. A total of 28,410 self-identified Aboriginal peoples were included in the 2012 APS.

Definition of ACO:

The primary outcome, ACO was defined by positive responses to both of the following questions “*Do you/Does(name) have Asthma diagnosed by a health professional?*” and “*Do you/Does (name) have chronic bronchitis, emphysema or chronic pulmonary obstructive disease or COPD diagnosed by a health professional?*”

Predictor Variables:

The 2012 APS collects a full range of information on demographic, environmental, socioeconomic and lifestyle factors. However, only those factors which have been associated with asthma, COPD and ACO in previous studies were considered in this study. Demographic variables consist of *Age, Sex and Marital Status*; Environmental variables include *Rural or Urban, Province, Dwelling – need repairs, Number of people in a household/Number of rooms in a dwelling*. Socio-economic variables consist of *Total Personal Income, Employment – the number of paid hours per week and Dwelling - owned or rented*. Lifestyle variables consisted of *Smoking Status and Smoking in the home*, and other diseases such as *Diabetes*.

This study was funded by the Seed, Bridge and Multi-Disciplinary Fund Committee and the Research and Graduate Studies, Memorial University of Newfoundland.

Statistical analysis:

Data analysis was conducted using SAS version 9.4. Mean/Standard Deviation and count/percent were used to summarize the study population for continuous and categorical variables, respectively. The differences in the continuous and categorical variables between males and females were examined by t-test and chi-square tests, respectively. Survey Logistic Regression was used to identify the significant risk factors for ACO in the univariate and multivariate analysis. To identify female-specific risk factors for ACO in the univariate and

multivariate analysis, the study population was stratified into a male and female group by a domain statement. Also, a trend test was carried out to test a linear relationship between the risk of ACO and the age variable. Sampling weights were included in all statistical analyses. Variances were estimated using 1,000 bootstrap weights to account for the complex survey design of the 2012 APS.

Results

Descriptive statistics:

As shown in Table 1, a total of 28,410 subjects without sampling weights represented 852,160 subjects with sampling weights (393, 000 males and 459, 160 females). Female aboriginal people have a significantly higher prevalence of ACO than males (3.53% vs 1.65%, $p < 0.0001$).

There were no significant differences in the distributions of age, province of residence, smoking status, smoking at home and history of diabetes between males and females. However, there was a significantly higher proportion of females who were widowed, separated and divorced (18%) vs males (8%), living in a dwelling in need of major repairs (14%) vs males (9%) and living in a dwelling with only 0-5 rooms (50%) vs males (48%). The data showed significantly higher proportions of males living in rural (26%) than females (23%), earning \$40,000 and over per year (32%) vs females (19%), living in rented dwellings (60%) vs females (55%) and working 80 hours and above per week (49%) vs females (46%).

Univariate Analysis

The results from the Univariate analysis are displayed in Table 2. The following factors were significantly associated with the risk of ACO in both males and females. Aboriginal people aged more than 45 years were significantly associated with a higher risk of ACO than those aged younger than 35 years. Aboriginal people who were *Widowed*, *Separated and Divorced* were significantly associated with a higher risk of ACO than those *Married or Living in common-law*.

In comparison to Aboriginal people living in *Quebec*, those living in other provinces and regions were significantly less likely to be associated with ACO. Aboriginal people residing in a *dwelling in need of major repairs* were three times more likely to be associated with ACO than those residing in a *dwelling that needs only regular maintenance*. Aboriginal

people living in a *dwelling with more than 6 rooms* were significantly associated with a lower risk of ACO than those living in a *dwelling with less than 5 rooms*.

Aboriginal people with an annual income *less than \$40,000* were at a significantly higher risk of ACO than those with an annual income of *\$5,000 or less*. In comparison to those who worked *0 to 40 hours* of paid hours per week, Aboriginal males who work *80 hours and over* were approximately three times more likely to be associated with increased risk for ACO while females who worked more than *40 hours* were also significantly associated with increased risk for ACO. Aboriginal peoples *living in rented dwellings* were three times more likely to be associated with ACO when compared to those *owning the dwelling*. Aboriginal people with a diagnosis of *Diabetes type 1 and 2* were three times more likely to be associated with ACO compared to those without the diagnosis of diabetes.

Daily smoking was associated with increased risk of ACO in comparison to those reporting *No smoking at all*. Aboriginal people reporting *smoking at home* were significantly associated with a higher risk of ACO in females only, not in males.

Multivariate Analysis

The results from the multivariate analysis are displayed in Table 3. The following factors were significantly associated with risk of ACO in both males and females. In comparison to those aged *12-34 years*, males aged *45 years and older* and females aged between *45 to 54 years* were significantly associated with a higher risk of ACO. A linear relationship between the risk of ACO and the age group variable was observed in males (trend test: $p < 0.0001$) but not in females (trend test: $p = 0.3226$). In comparison to those from Quebec, males from *Atlantic and Territories region* and *British Columbia* and females from *Atlantic and Territories region*, *Prairies* and *British Columbia* were significantly less likely to be associated with ACO.

Aboriginal people living in a *dwelling in need of major repairs* were more than two times more likely to be associated with ACO compared to those living in a *dwelling in need of regular maintenance* in both males and females. Aboriginal people living in a *rented dwelling* were approximately two times more likely to be associated with ACO than those *owning a dwelling* in both males and females.

The following factors were significantly associated with risk of ACO in females only. Aboriginal females who smoked daily were two times more likely to be associated with ACO compared to those that do not smoke at all. No such association was observed in males. Aboriginal females with a diagnosis of *Diabetes (type 1 and 2)* were also approximately three

times more likely to be associated with ACO compared to those without the diagnosis of diabetes. No such association was observed in males. Aboriginal females who are *widowed, separated or divorced* are two times more likely to be associated with ACO compared to those who are either *married or living in common law*. No such association was observed in males. Males working *80 hours and over* and females working *40 hours and over* were significantly associated with increased risk of ACO when compared to those working *0 to 40 hours per week*.

Discussion

This study used the Aboriginal Peoples Survey 2012, which was carried out by Statistics Canada. It was a cross-sectional survey design in which 28,410 subjects were interviewed either by telephone or mail. This data set also had a good response rate of 76%. The outcome of our study, ACO, was defined based two questions on diagnosis of asthma and COPD as part of the APS 2012 data. We have reported that several factors including age, province of residence, dwelling in need of repairs, number of paid hours per week and dwelling – owned or rented are significantly associated with the risk of ACO in both Aboriginal males and females which are consistent with the results reported by our team in a previous paper.² In this study, we have identified four female-specific risk factors (a current daily smoker, having a diagnosis of type 1 or 2 diabetes, being widowed, separated or divorced and working above 40hrs a week) which are significantly associated with the risk of ACO.

Smoking is a well-recognized risk factor for many chronic respiratory diseases and females are more predisposed to the negative influence of smoking than males.¹⁸⁻²⁰ A population-based study reported that among individuals who smoked ≥ 10 years, the prevalence of ACO was significantly higher in women than men.¹⁸ Similar association between smoking pack-years and the risk of Chronic Bronchitis was reported in two First Nations communities in Saskatchewan, Canada for 36 years and older females.²⁰ Results from our study showed that aboriginal females had a higher prevalence of ACO than aboriginal males in all the age groups. Although biological mechanisms of increased risk of chronic respiratory diseases associated with cigarette smoking is still unknown, studies showed female hormones, most especially estrogen, may accelerate metabolism of cigarette smoke, possibly through the CYP (Cytochrome P450) pathways, into various metabolites.

However, because estrogen does not modify detoxifying enzymes such as glutathione S-transferase, female smokers experience increased oxidative stress in the lungs, which may lead to lung diseases such as ACO or COPD.^{21,22}

Increased risk of diabetes type 1 and 2 has been associated with chronic respiratory diseases in many population studies.²³⁻²⁶ However, sex-specific association has been rarely reported. Our results showed that females with either type 1 or 2 diabetes were approximately three times more likely to be associated with ACO; however this association was not observed in males. A retrospective cohort study showed that female COPD patients of all ages with exacerbations showed significantly increased risk of developing diabetes.²⁷ A similar study of patients hospitalized for COPD exacerbation in Spain also reported that female COPD patients had a higher prevalence of diabetes when compared to their male counterparts.²³ However, another population study from Sweden reported that males aged 45 years and above have an increased risk of diabetes type 2 compared to females,²⁴ but females are more predisposed to diabetes type 1 than males.²⁵ Even though the mechanism for increased risk of diabetes in female COPD or chronic respiratory diseases remains unclear, we suggest that systemic inflammation might be a probable explanation. In patients with COPD, the increased serum levels of inflammatory mediators are significantly associated with a higher risk of diabetes type 2.^{28,29} Studies also show increased risk of diabetes in female COPD patients might relate to side effects of COPD medications such as systemic glucocorticoid therapy which showed distinct differences in glucocorticoid signalling pathway between males and females.³⁰⁻³²

There are fewer studies investigating the female-specific association between marital status and chronic respiratory diseases. A study from the US concluded that female subjects under the age of 70 years who remarried after a divorce or bereavement had a significantly decreased risk of developing COPD.³³ This could be due to marriage acting as a health promoting effect, as marital status in relation to grief, alteration of smoking habits and change in socioeconomic status (personal income) could be related to the incidence of smoking related diseases such as COPD and ACO.^{33,34} To our knowledge, our study is the first paper to investigate the effects of marital status and a new disease, ACO, among Aboriginal people. Our results suggest that Aboriginal females who are widowed, separated or divorced are two times more likely to be associated with ACO, and this was not observed in males. Finally, in our study, we found that females working *40 hours and over* were significantly associated with increased risk of ACO. Sex- related hormones and gender differences in risk and severity of many lung diseases have been long recognized and they also play an important

role in their pathophysiology.^{11,12} Epidemiological evidence has reported significant differences in lung diseases before and after menopause when sex related hormones undergo significant changes.^{13,15,35,36} A recent study reported a significant association between Toll-like receptors (human innate immune system) and lung function in female swine workers only, not in male swine workers and the association was only observed among young female workers. This study concluded that the involvement of female related hormones in the aetiology of many lung diseases could be due to occupational exposure.³⁵

Limitations

Due to the size of our study population, it will not be feasible to perform a spirometry test. Identification of ACO cases based on patients with diagnosis of both asthma and COPD is subject to misclassification. However, it has been used in other large population studies.^{4,37-}

³⁹ Self-reported questionnaires using self-reported health conditions diagnosed by a health professional have also been widely used in many large population surveys with reasonable sensitivity and specificity.^{18,40-42} Work exposure information is not available in our data, which limits our further investigation on possible dose-response relationship.

Conclusion

This study has identified many risk factors for ACO for both males and females and includes age, province, long hours at work, living in rented dwelling and dwelling in need of major repairs. It also highlights female-specific risk factors for ACO, which includes smoking status, marital status and diabetes. The results of our study may provide useful information for future development of prevention and public health intervention programs in aboriginal communities to reduce the burden of ACO.

Disclaimer

The analysis presented in this paper was conducted at the Memorial University Research Data Centre which is part of the Canadian Research Data Centre Network (CRDCN). The services and activities provided by the Memorial University Research Data Centre are made possible by the financial or in-kind support of the SSHRC, the CIHR, the CFI, Statistics Canada, Seed, Bridge, Multidisciplinary Fund Committee and Memorial University. The views expressed in this paper do not necessarily represent the CRDCN's or that of its

partners. This study was approved by the Newfoundland and Labrador Health Research Ethics Board.

Declaration of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Table 1 (Descriptive Analysis stratified into Males and Females)

Variables	Labels	Males (%) (n = 393,000)	Females (%) (n = 459,160)	p value
ACO	Yes	1.65	3.53	<0.0001
Age	12 to 34 years	47	44	0.3214
	35 to 44 years	17	18	
	45 to 54 years	17	18	
	55 to 64 years	12	12	
	65 years and over	7	8	
Marital Status	Married and Living in common-law	51	45	<0.0001
	Widowed, Separated and Divorced	8	18	
	Single, never married	41	37	
Rural or Urban	Rural area	26	23	0.0055
	Small population centre	21	21	
	Medium population centre	11	12	
	Large urban population centre	42	44	
Total Personal Income	\$5,000 or less income	27	24	<0.0001
	\$5,001 to \$19,999	19	29	
	\$20,000 to \$39,999	22	28	
	\$40,000 and over	32	19	
Province of residence	Atlantic and Territories*	11	11	0.3862
	Quebec	11	10	
	Ontario	24	25	
	Prairies	37	37	
	British Columbia	17	17	
Smoking Status	Daily	27	28	0.6987
	Occasionally	9	9	
	Not at all	64	63	
Anybody smoking at home	Yes	19	20	0.3089
	No	81	80	
Dwelling (Owned/Rented)	Owned	40	45	<0.0001
	Rented	60	55	
Dwelling in need of major repairs	Yes, major repairs are needed	9	14	<0.0001
	Yes, minor repairs are needed	26	26	
	No, only regular maintenance is needed	65	60	
Diabetes	Diabetes type 1 and type 2	9	9	0.8780
	Gestational and no diagnosis of diabetes	91	91	

How many rooms are there in a dwelling	0 and 5 rooms	48	50	0.0308
	6 and 8 rooms	31	32	
	9 rooms and over	21	18	
Number of paid hours per week	0 to 40 hours	47	39	<0.0001
	41 to 79 hours	4	15	
	80 hours and over	49	46	

Number of participants without sample weights: 28,410

Number of participants with sample weights: 852,160 (393,000 males and 459,160 females)

*: including Nova Scotia, Newfoundland and Labrador, Prince Edward Island, New Brunswick, Nunavut, Yukon, Northwest Territories

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Table 2 (Univariate Analysis stratified into Males and Females)

Variables	Males		Females	
	% of ACO	Odds Ratio (95% CI)	% of ACO	Odds Ratio (95% CI)
Age				
35 to 44 years	0.79	0.94 (0.32 – 2.76)	2.39	1.07 (0.57 – 2.02)
45 to 54 years	1.87	2.21 (1.07 – 4.53)	6.25	2.93 (1.59 – 5.38)
55 to 64 years	3.90	4.71 (2.32 – 9.58)	4.61	2.12 (1.16 – 3.89)
65 years and over	4.30	5.22 (2.66 – 10.25)	5.36	2.48 (1.23 – 5.01)
12 to 34 years	0.85	1	2.23	1
Marital Status				
Widowed, Separated and Divorced	4.62	3.61 (1.75 – 7.44)	7.59	3.36 (2.00 – 5.64)
Single, never married	1.79	1.36 (0.77 – 2.41)	3.41	1.45 (0.95 – 2.21)
Married and Living common-law	1.32	1	2.39	1
Rural or Urban				
Rural area	1.71	0.98 (0.53 – 1.79)	2.62	0.64 (0.38 – 1.07)
Small population centre	1.15	0.66 (0.32 – 1.36)	2.73	0.67 (0.42 – 1.06)
Medium population centre	2.18	1.25 (0.55 – 2.85)	4.69	1.16 (0.64 – 2.12)
Large urban population centre	1.74	1	4.05	1
Total Personal Income				
\$5,000 or less income	1.16	1.26 (0.56 – 2.87)	2.57	1.86 (1.04 – 3.33)
\$5,000 to \$19,999	2.66	2.94 (1.33 – 6.45)	5.15	3.81 (2.28 – 6.36)
\$20,000 to \$39,999	2.41	2.65 (1.23 – 5.74)	4.21	3.08 (1.59 – 5.94)
\$40,000 and over	0.92	1	1.41	1
Province of residence				
Atlantic and Territories**	0.79	0.17 (0.07 – 0.41)	1.31	0.18 (0.11 – 0.34)
Ontario	1.72	0.38 (0.18 – 0.81)	4.78	0.68 (0.37 – 1.25)
Prairies	1.32	0.29 (0.14 – 0.62)	2.99	0.42 (0.24 – 0.72)
British Columbia	1.12	0.24 (0.11 – 0.57)	2.38	0.33 (0.18 – 0.61)
Quebec	4.38	1	6.89	1
Type of Smoker				
Daily	2.46	2.00 (1.16 – 3.44)	6.12	2.60 (1.75 – 3.87)
Occasionally	1.46		3.15	1.30 (0.67 – 2.55)

Not at all	1.24	1.19 (0.46 – 3.08) 1	2.45	1
Anybody smoking at home Yes No	1.13 1.46	0.77 (0.43 – 1.40) 1	6.51 2.44	2.78 (1.80 – 4.29) 1
Dwelling (Owned/Rented) Rented Owned	2.53 0.99	2.59 (1.55 – 4.33) 1	5.32 2.11	2.60 (1.76- 3.85) 1
Dwelling in need of major repairs Yes, major repairs are needed Yes, minor repairs are needed No, only regular maintenance is needed	3.31 1.71 1.31	2.56 (1.40 – 4.68) 1.30 (0.72 – 2.38) 1	8.24 3.11 2.65	3.31 (1.96 – 5.56) 1.18 (0.76 – 1.82) 1
Diabetes Diabetes type 1 and type 2 Gestational and no diagnosis of diabetes	4.93 1.34	3.81 (2.07 – 6.95) 1	9.17 3.01	3.26 (2.04 – 5.21) 1
How many rooms are there in a dwelling 6 and 8 rooms 9 rooms and over 0 and 5 rooms	1.03 2.59 2.56	0.39 (0.21 – 0.79) 0.57 (0.23 – 1.38) 1	2.59 0.98 5.06	0.51 (0.26 – 0.95) 0.19 (0.09 – 0.38) 1
Number of paid hours per week 41 to 80 hours 80 hours and over 0 to 40 hours	1.58 2.33 0.95	1.67 (0.69 – 4.03) 2.48 (1.41 – 4.36) 1	3.74 5.67 1.41	2.73 (1.18 – 6.31) 4.21 (2.79 – 6.37) 1

*: including Nova Scotia, Newfoundland and Labrador, Prince Edward Island, New Brunswick, Nunavut, Yukon, Northwest Territories

Table 3 (Multivariate Analysis stratified into Males and Females)

Variables	Male	Female
	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Age		
35 to 44	1.07 (0.38 – 3.01)	0.94 (0.48 – 1.83)
45 to 54	2.30 (1.09 – 4.85)	2.39 (1.18 – 4.85)
55 to 64	4.42 (1.89 – 10.35)	1.15 (0.46 – 2.86)
65 and over	4.99 (1.98 – 12.59)	0.98 (0.34 – 2.84)
12 to 34	1	1
Marital Status		
Widowed, Separated and Divorced	1.95 (0.91 – 4.23)	2.20 (1.17 – 4.16)
Single, never married	1.96 (0.97 – 3.97)	1.46 (0.92 – 2.32)
Married and Living common-law	1	1
Province of residence		
Atlantic and Territories*	0.23 (0.09 – 0.56)	0.15 (0.07 – 0.31)
Ontario	0.58 (0.25 – 1.37)	0.62 (0.34 – 1.12)
Prairies	0.49 (0.21 – 1.13)	0.41 (0.23 – 0.69)
British Columbia	0.36 (0.14 – 0.90)	0.34 (0.18 – 0.66)
Quebec	1	1
Type of Smoker		
Daily	1.36 (0.74 – 2.50)	1.83 (1.16 – 2.90)
Occasionally	1.11 (0.41 – 3.08)	0.81 (0.35 – 1.84)
Not at all	1	1
Dwelling (Owned/Rented)		
Rented	2.27 (1.33 – 3.89)	1.70 (1.13 – 2.58)
Owned	1	1
Dwelling in need of major repairs		
Yes, major repairs are needed	2.66 (1.37 – 5.15)	2.59 (1.49 – 4.52)
Yes, minor repairs are needed	1.09 (0.56 – 2.10)	1.31 (0.85 – 2.02)
No, only regular maintenance is needed	1	1
Diabetes		
Diabetes type 1 and type 2	1.56 (0.79 – 3.07)	2.46 (1.52 -3.99)
Gestational and no diagnosis of diabetes	1	1
Number of paid hours per week		
41 to 80 hours	1.94 (0.79 – 4.77)	3.11 (1.29 – 7.45)
81 hours and over	1.89 (1.05 – 3.41)	4.11 (2.52 – 6.36)
0 to 40 hours	1	1

*: including Nova Scotia, Newfoundland and Labrador, Prince Edward Island, New Brunswick, Nunavut, Yukon, Northwest Territories