BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020656
Article Type:	Research
Date Submitted by the Author:	15-Nov-2017
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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	lung function, gender, smoking, antioxidant vitamins

Effects of dietary antioxidant vitamins on lung functions according to gender and smoking status: KNHANES 2007–2014

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Abstract

Objective: Cigarette smoke-induced oxidative stress plays an important role in the pathogenesis of chronic obstructive pulmonary disease (COPD). Dietary antioxidants are thought to prevent smoke-induced oxidative damage. The aim of this study was to investigate associations between lung function and the consumption of antioxidant vitamins in Korean adults.

Methods: In total, 21,148 participants from the Korean National Health and Nutrition Examination Survey (2007–2014) were divided into four groups based on smoking history and gender. Multivariate regression models were used to evaluate associations between lung function and intake of dietary antioxidants.

Results: Subjects in the highest-intake quintile (Q5) of vitamin A, carotene, and vitamin C intake had mean forced expiratory volume in 1 second (FEV_1) measurements that were 25 ml, 27 ml, and 36 ml higher than those of individuals in the lowest-intake quintile (Q1), respectively (*P* for trend; *P*=0.032, *P*=0.038, and *P*=0.004, respectively). The risks of COPD for male smokers in Q1 increased 5.42-fold (95% CI=4.09–7.18), 5.27-fold (95% CI=3.98–6.98), and 5.61-fold (4.26–7.39) for vitamin A, carotene, and vitamin C, respectively, compared to those of female non-smokers in Q5. Among COPD patients, males who smoked >20 pack years had mean FEV_1 measurements that were 124 ml, 94 ml, and 113 ml higher than those of patients in Q1 (*P* for trend; *P*=0.018, *P*=0.026, and *P*=0.047, for vitamin A, carotene, and vitamin C, respectively).

Conclusions: These findings indicate that the influence of antioxidant vitamins on lung function depends on gender and smoking status in the Korean COPD population.

Keywords: lung function, gender, smoking, antioxidant vitamins

Strengths and limitation of this study

- This study revealed that the influence of antioxidant vitamins on lung function depends on gender and smoking status in Korean patients with COPD.
- A cross-sectional study with a large sample size collected from a national health survey
- Main limitations include a possible recall bias and no further verification of nutritional intake.

Introduction

Chronic obstructive pulmonary disease (COPD) causes morbidity and mortality[1]. Smoking is a primary risk factor for COPD; however, other factors also contribute as only 10–20% of smokers develop airflow limitations[2].

Dietary antioxidants protect against oxidative stress caused by smoking[3], and multiple studies have revealed associations between the intake of antioxidant vitamins or fibers and respiratory diseases[4-8]. However, evidence supporting the benefits of vitamin supplement therapy is lacking[9-11].

Because micronutrient status is affected by dietary intake and metabolic turnover, which are regulated by oxidative stress, the benefits of antioxidant vitamins may vary by gender and smoking status. Multiple studies have shown that different antioxidants exhibit different effects based on smoking status. Morabia *et al*. reported an association between airway obstruction and vitamin A intake in smokers compared to former smokers, whereas Hu *et al*. reported that carotene was less strongly associated with FEV_1 in smokers compared to former smokers and non-smokers[12 13].

This study used KNHANES data to investigate whether dietary antioxidant vitamins were independently associated with pulmonary function and COPD in the Korean population. This study also evaluated whether the effects of antioxidant vitamins on pulmonary function differed based on gender or smoking status.

Patients and Methods

Study population

Participants were sampled from Korean National Health and Nutritional Examination Survey (KNHANES; 2007–2014) IV–VI, a nationwide survey designed to be representative of the population that is used to establish health policies. KNHANES contains a massive database with information about demographic characteristics, comorbidities, lung function, nutritional status, and health (https://knhanes.cdc.go.kr/knhanes).

A two-stage stratified systemic sampling method was use to select 65,973 individuals to survey between February 2007 and December 2014. Of the chosen individuals, 34,278 participants over 40 years of age responded to questionnaires regarding diet and smoking history and underwent a medical examination. After excluding subjects who omitted lung function or nutrition data, we analyzed data from 21,148 (8,804 men and 12,344 women) in this study. This study was approved by the Institutional Review Board of the Korean Centers for Disease Control and Prevention. All participants provided informed written consent.

Spirometry and airflow obstruction definitions

The pulmonary function test (PFT) was performed using dry-rolling seal volume spirometers (Model 2130; SensorMedics, Yorba Linda, CA, USA) and standardized according to the American Thoracic Society/European Respiratory Society criteria[14]. Qualified technicians and principal investigators assessed the spirometry data for acceptability and reproducibility. The predictive equations for the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) were derived from survey data on non-smokers who had normal chest X-rays and no previous history of respiratory diseases[15]. COPD was defined as a $FEV_1/FVC < 70\ \%$[16].

Dietary assessments

Food intake data were obtained using the 24-h recall method, in which participants were asked to report the foods and amounts thereof consumed during the previous 24 hours. Total energy (kJ/d (kcal/d)) and total intake of antioxidant vitamins were calculated using the Korean Food Composition Table[17] as the reference. Antioxidant vitamin consumption was adjusted for total energy intake.

Potential confounders

Data regarding demographic information, education level, household income, smoking status, smoking amount, alcohol intake, body mass index (BMI), and comorbid diseases were obtained. Educational level was categorized as elementary school or lower, completion of middle school, completion of high school, and college or higher. Household income was divided by quartile.

Smokers were subjects who smoked more than 100 cigarettes in their lifetime. Participants were categorized in terms of smoking status as follows: smoker, ex-smoker, or never smoked. The smoking amount was determined in pack years, which was calculated by multiplying the duration of smoking (years) by the number of packs of cigarettes smoked. Comorbid diseases included hypertension, stroke, cardiovascular disease, arthritis, tuberculosis, asthma, diabetes mellitus, thyroid disorders, renal failure, liver disease, and malignancy.

Statistical analysis

The relationship between antioxidant vitamin intake and lung function was analyzed using multiple linear regression analyses. We analyzed the energy-adjusted antioxidant vitamin intake by quintiles. The adjustment factors were age, sex, BMI, educational level, household income, total energy intake, number of comorbid diseases, smoking history, alcohol intake, and pack years[4 12 18]. Assessments of linear trends across increasing antioxidant vitamin quintiles were also performed.

We estimated the odds ratios (ORs) of COPD using multivariate logistic regression analyses of quintiles after adjusting for confounding factors. Participants were divided into four groups based on

gender and smoking status (male smokers, male non-smokers, female smokers, female non-smokers). For combined analyses between the effects of antioxidant vitamin intake, gender, and smoking status on the risk of COPD, interaction tests were performed. Multiple linear regression analyses were performed after categorizing COPD patients by smoking status and amount.

Statistical analyses were performed using PASW Statistics ver. 20 (SPSS Inc., Chicago IL, USA) and SAS ver. 9.4 (SAS Institute, Cary, NC, USA) software. *P*-values <0.05 were considered statistically significant.

Results

The baseline characteristics of the 21,148 participants are shown in Table 1. All subjects were classified into four groups based on smoking history and gender. Of the 7,986 smokers, 7,178 were male (mean age, 57.8±11.0 years) and 808 were female (mean age, 57.4±12.5 years). Of the 13,162 individuals who had never smoked, 1,626 were male (mean age, 57.9±11.3 years) and 11,536 were female (mean age, 57.1±10.8 years). Among all subjects, 3,005 were diagnosed with COPD. The prevalence of COPD was highest in male smokers (26.4%) and lowest in female non-smokers (6.4%). The four groups differed regarding age, BMI, educational level, household income, and alcohol usage (P<0.001). Energy intake was significantly higher in males than females (males, 2,256.5 kcal; females, 1,648.3 kcal; P<0.001). The levels of vitamin A, carotene, and vitamin C were highest in the male non-smoker group and lowest in the female smoker group.

A statistically significant dose–response relationship was observed between lung function (FEV_1, FVC) and dietary antioxidant vitamin levels (Table 2). Participants in the highest quintile (Q5) of vitamin A intake had 25 ml higher FEV_1 (P for trend across quintiles = 0.032) and 31 ml higher FVC (P for trend across quintiles = 0.013) compared to participants in the lowest quintile (Q1). Participants in Q5 for carotene intake had 27 ml higher FEV_1 (P for trend across quintiles = 0.038) and 34 ml higher FVC (P for trend across quintiles = 0.011) measurements compared to participants in Q1. Participants in Q5 of vitamin C intake had 36 ml higher FEV_1 (P for trend across quintiles = 0.004) and 35 ml higher FVC (P for trend across quintiles = 0.027) measurements compared to participants in Q1.

The effects of gender, smoking, and dietary antioxidant vitamins on the risk of COPD are summarized in Table 3. The risk of COPD for male smokers in Q1 for vitamin A, carotene, and vitamin C intake increased by 5.42-fold (95% CI=4.09–7.18), 5.27-fold (95% CI=3.98–6.98), and 5.61-fold (95% CI=4.26-7.39), respectively, which was greater than that observed for female non-smokers in Q5 for antioxidant vitamin intake. The interaction effect was significant (all P-values <0.001).

According to the multivariate logistic regression analyses, the risk of COPD was influenced by dietary antioxidant vitamin levels in male smokers (Figure 1). In male smokers, the risk of COPD in subjects in Q5 for vitamin A and vitamin C intake was significantly lower than that for subjects in Q1 (vitamin A, OR = 0.77, 95% CI = 0.63–0.94, *P* = 0.011; vitamin C, OR = 0.76, 95% CI = 0.62–0.93, *P* = 0.007). Similarly, the prevalence of COPD was lower in Q5 compared to Q1 for carotene; however, this trend was not significant (OR = 0.82, 95% CI = 0.67–1.00, *P*=0.052). The prevalence of COPD did not increase significantly as the intake of dietary antioxidant vitamins increased in male non-smokers, female smokers, or female non-smokers. No significant interaction between the effects of antioxidant vitamins on COPD and smoking status was observed. The correlation between the risk of COPD and antioxidant vitamin intake was stronger in male smokers who smoked less than 20 pack years (not shown).

We investigated the association between dietary antioxidant vitamin intake and lung function after limiting the analyses to individuals with COPD. The changes in FEV_1 were not statistically significant based on the levels of dietary antioxidant vitamins in subjects with COPD. Interestingly, only male smokers exhibited a beneficial association between dietary antioxidant vitamin intake and FEV_1 (Table 4). Male smokers with COPD in Q5 for vitamin A intake had a 66-ml higher FEV_1 (*P* for trend across quintiles = 0.024) compared to those in Q1. Male smokers with COPD in Q5 of carotene and vitamin C intake had 65-ml higher FEV_1 (*P* for trend across quintiles = 0.046) and a 101-ml higher FEV_1 (*P* for trend across quintiles = 0.039), respectively, compared to individuals in Q1.

Male COPD patients who had smoked ≥20 pack years exhibited a beneficial association between dietary antioxidant vitamin intake and FEV_1 (Figure 2). Male COPD patients in Q5 of vitamin A intake who had smoked ≥ 20 pack years had a 124-ml higher FEV_1 (*P* for trend across quintiles = 0.018) compared to individuals in Q1. COPD patients in Q5 of carotene intake who had smoked ≥20 pack years had a 94-ml higher FEV_1 (*P* for trend across quintiles = 0.026) compared with patients in

Q1. COPD patients in Q5 of vitamin C intake who had smoked >20 pack years had a 113-ml higher FEV_1 (*P* for trend across quintiles = 0.047) compared to patients in Q1.

Discussion

This study examined the association between the intake of antioxidant vitamins and lung functions in the Korean population. Previous studies showed that antioxidant vitamins, including vitamin C, were protective of the human lung [5 13], whereas high levels of vitamin A and carotene were also associated with increased lung functions in multiple studies[12 19-23]. In a randomized controlled trial, Keranis *et al*. reported that increasing the intake of antioxidants improved lung function[24].

Cigarette smoking is the primary cause of COPD as it increases oxidative stress in the lungs and activates inflammatory responses[25]. Notably, one inhalation from a cigarette generates more than 10^{15} free radicals and other oxidants[26].

Antioxidants protect against the damage caused by smoking in multiple ways[3]. For example, as it is water-soluble, vitamin C scavenges free radicals in the cytoplasm. Koike *et al*. reported that vitamin C diminished smoke-induced oxidative stress and corrected emphysematous lungs *in vivo*[27].

Carotenoids quench singlet oxygen and inhibit lipid peroxidation[3]. In an animal study, the respiratory epithelia of retinol-deficient animals had atrophied ciliated cells and modified lipid contents[28]. The pathologic features of the retinol-deficient animals were similar to those of human smokers[29].

Smokers exhibit nicotine-induced reductions in intestinal absorption and elevated metabolic turnover[30]. The metabolism or destruction of antioxidant vitamins increases in inflammatory environments[31-34], which suggests that smokers with COPD require larger amounts of antioxidant vitamins to achieve the same blood levels as non-smokers. A study by Sargeant found that vitamin C may modify the adverse effects of smoking and the risk of COPD in the European population[35]. Additionally, Shin *et al.* reported that Korean smokers with adequate vitamin C intake had acceptable pulmonary functions[36]. Additionally, Morabia *et al.* identified that airway obstruction was reduced by vitamin A in smokers[12].

One notable finding in the current study was that the effects of antioxidant vitamin intake on lung

function were stronger among male smokers. Additionally, the association between the risk of COPD and antioxidant vitamin intake was clear for male but not female smokers. Male smokers with lower antioxidant vitamin intakes had increased ORs of COPD compared to female smokers. After limiting the analysis to subjects with COPD, a significant association between antioxidant vitamin intake and FEV_1 was observed in male smokers but not in other groups. This finding was similar to that of Joshi *et al.,* where changes in COPD risk and dietary vitamin C and vitamin E intake differed between males and females [37].

It is not known how gender differences impact pulmonary functions based on antioxidant vitamin intake; however, animal studies have revealed gender differences in antioxidant vitamin requirements. Al Rejaie *et al.* reported gender-related differences in the protective roles of ascorbic acid against oxidative stress[38], whereas Jiao *et al*. revealed gender differences in the regulation and expression of oxidative genes in mice [39].

Studies detailing the effects of antioxidant vitamins on lung function in smokers and non-smokers are lacking [5 23]. In the US population, Britton *et al.* revealed that the relationship between vitamin C intake and FEV_1 was stronger in ex-smokers than non- or current smokers[5]. Shahar *et al*. reported a relationship between individuals in Q1 of vitamin A intake and airway obstruction among individuals who smoked >41 pack years [23].

Among male COPD patients, those smoking ≥20 pack years had improved lung functions as antioxidant vitamin intake increased. These results support that associations between antioxidants and lung function may differ according to smoking status in COPD patients. However, it is unknown what causes such differences. One hypothesis is that the efficacy of antioxidant vitamins is proportional to the level of oxidant burden in COPD. Additional studies are required to determine whether the benefits of antioxidant vitamins depend on the smoking duration or dose in COPD patients.

This study has several limitations that should be noted. As we used a cross-sectional design, the data cannot be used to answer questions regarding causation. Additionally, because data on nutritional

intake were obtained by 24-hour recall, inaccurate responses may have been offered. This study used the pre-bronchodilator FEV_1 for determining COPD; however, the definition of COPD is based on post-bronchodilator FEV_1[16]. This study failed to obtain data regarding air pollution or occupational exposure and, therefore, could not associate these variables with lung function; however, the strength of this study is that these data represent the Korean population.

Conclusion

This study supports that antioxidant vitamins have beneficial effects on pulmonary function in the Korean population. The data indicate that there is a stronger association between antioxidant vitamin intake and the risk of COPD in male smokers. The beneficial effects of antioxidant vitamins in COPD patients differed by gender and smoking status, and future investigations should determine the roles of dietary antioxidant vitamins in specific groups.

Contributors

JYH and YSK equally contributed to the conception and design of the research; YSK contributed to the design of the research; CYL contributed to the acquisition and analysis of the data; MGL and YSK contributed to the interpretation of the data; and JYH drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding

This research was supported by the National Research Foundation of Korea Grant funded by Korean Government (NRF 2017R1C1B5017879, NRF-2017M3A9E8033225).

Competing interests

None declared

Provenance and peer review

Not commissioned; externally peer reviewed

Data sharing statement

No additional data are available.

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Table legends

Table 1. Study population characteristics.

¶, numbers represent mean percentages (standard deviation).

Table 2. Mean values of adjusted lung function measurements across quintiles of vitamin A, carotene, and vitamin C intake.

Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases, alcohol consumption, smoking history, pack years (smoking amount), household income, and education level.

P values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.

Table 3. Association between vitamin A, carotene, and vitamin C intake and COPD according to gender and smoking status.

OR was determined following adjustment for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level.

¶, The risk for COPD was significantly different between Q1 and Q5.

Table 4. Mean values of adjusted forced expiratory volume in 1-second (FEV_1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.

Adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level.

P values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.

Figure Legends

Figure 1. Odds ratios for the association between antioxidant vitamin intake and COPD among (a) male and (b) female smokers and non-smokers.

Odds ratios were adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level.

Figure 2. Mean values of adjusted forced expiratory volume in 1-second (FEV_1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD patients according to smoking status.

Values were adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level. *P*-values were determined using tests for linear trends across increasing quintiles (median) of antioxidant vitamin intake.

Table 1. Study population characteristics

	Total (n=21,148)	Male smokers (n=7,178)	Male non-smokers (n=1.626)	Female smokers (n=808)	Female non-smokers (n=11,536)	*P* value
Age ¶	57.4 (10.9)	57.8 (11.0)	57.9 (11.3)	57.4 (12.5)	57.1 (10.8)	<0.001
40–49	6048 (28.6)	1998 (27.8)	464 (28.5)	273 (33.8)	3313 (28.7)	<0.001
50–59	6131 (29.0)	1981 (27.6)	431 (26.5)	199 (24.6)	3520 (30.5)	
60–69	5387 (25.5)	1913 (26.7)	430 (26.4)	158 (19.6)	2866 (25.0)	
70–	3582 (16.9)	1286 (17.9)	301 (18.5)	178 (22.0)	1817 (15.8)	
BMI¶	24.2 (3.0)	24.2 (2.8)	24.3 (2.8)	23.8 (3.6)	24.2 (3.2)	0.007
Education						<0.001
Elementary	7229 (34.2)	1763 (24.6)	321 (19.7)	381 (47.2)	4764 (41.3)	
Middle school	3315 (15.7)	1216 (16.9)	267 (16.4)	112 (13.9)	1720 (14.9)	
High school	6427 (30.4)	2366 (33.0)	458 (28.2)	228 (28.2)	3375 (29.3)	
More than college	4169 (19.7)	1831 (25.5)	580 (35.7)	87 (10.8)	1671 (14.5)	
Household income						<0.001
1st quartile	4763 (22.5)	1440 (20.1)	289 (17.8)	315 (39.0)	2719 (23.6)	
2nd quartile	5427 (25.7)	1874 (26.1)	391 (24.1)	223 (27.6)	2939 (25.5)	
3rd quartile	5162 (24.4)	1869 (26.1)	414 (25.5)	145 (17.9)	2734 (23.7)	
4th quartile	5780 (27.3)	1988 (27.7)	530 (32.6)	125 (15.5)	3137 (27.2)	
Comorbidity¶	0.9 (1.1)	0.9 (1.0)	0.8 (0.9)	1.0 (1.2)	1.0 (1.1)	<0.001
Pack years¶	4.7 (13.6)	13.3 (20.3)	0.2 (2.2)	3.3 (11.9)	0.0 (0.0)	<0.001
Alcohol	17554 (83.0)	6877 (95.8)	1399 (86.0)	714 (88.4)	8564 (74.2)	<0.001
Energy intake (Kcal/day)¶	1901.5 (797.8)	2266.5 (869.7)	2212.6 (855.9)	1538.2 (653.4)	1656.0 (630.0)	<0.001
Vitamin A (μg RE/day)¶	822.5 (1118.5)	881.9 (1067.5)	925.5 (1095.2)	600.3 (644.2)	786.6 (1173.9)	<0.001
Carotene (μg/day)¶	4337.3 (6206.0)	4596.2 (5557.8)	4803.8 (5506.6)	3143.5 (3682.6)	4194.1(6780.6)	<0.001
Vitamin C (mg/day)¶	111.9 (107.6)	111.8 (97.9)	128.8 (107.1)	84.8 (96.9)	111.5 (113.5)	<0.001
FEV_1 (ml)¶	2.60 (0.67)	3.02 (0.68)	3.09 (0.66)	2.23 (0.56)	2.30 (0.46)	<0.001
FVC (ml)¶	3.38 (0.84)	4.07 (0.72)	4.04 (0.73)	2.88 (0.62)	2.89 (0.51)	<0.001
FEV1/FVC (%)¶	77.3 (7.9)	73.9 (9.1)	76.6 (7.9)	77.2 (8.0)	79.5 (6.1)	<0.001
COPD	3,005 (14.2)	1893 (26.4)	256 (15.7)	119 (14.7)	737 (6.4)	<0.001

¶, numbers represent mean percentages (standard deviation).

Table 2. Mean values of adjusted lung function measurements across quintiles of vitamin A, carotene, and vitamin C intake.

	Q1	Q2	Q3	Q4	Q5	Difference between Q5 and Q1 (95% CI)	*P* value for trend
Vitamin A							
Mean intake (μg RE)	151.2	353.6	573.1	893.9	2140.8		
FEV_1 (ml)	2379	2388	2406	2395	2404	25 (5,45)	0.032
FVC(ml)	3119	3135	3156	3148	3150	31 (7,54)	0.013
Predicted FEV_1 (%)	91.37	91.39	91.79	91.37	91.77	0.40 (-0.24,1.04)	0.393
Predicted FVC (%)	90.93	91.02	91.38	91.18	91.4	0.47 (-0.08,1.02)	0.326
Carotene							
Mean intake (μg)	691.1	1747.4	2938.9	4736.1	11574.1		
FEV_1 (ml)	2347	2361	2373	2367	2374	27 (8,47)	0.038
FVC (ml)	3088	3115	3125	3118	3122	34(11.57)	0.011
Predicted FEV_1 (%)	91.55	91.96	92.16	91.75	92.16	0.61 (-0.17,1.24)	0.203
Predicted FVC (%)	91.02	91.63	91.71	91.36	91.74	0.72 (0.18,1.26)	0.032
Vitamin C							
Mean intake (mg)	24.2	53.6	84.2	128.8	268.9		
FEV_1 (ml)	2411	2421	2433	2436	2447	36 (16.56)	0.004
FVC (ml)	3117	3121	3131	3137	3152	35 (12.58)	0.027
Predicted FEV_1 (%)	91.3	91.43	91.79	91.82	92	0.70 (0.67,1.33)	0.169
Predicted FVC (%)	91.29	91.29	91.52	91.68	91.91	0.62 (0.75,1.16)	0.118

Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases, alcohol consumption, smoking history, pack years (smoking amount), household income, and education level. *P* values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.

Table 3. Association between vitamin A, carotene, and vitamin C intake and COPD according to gender and smoking status.

	Intake		COPD		OR		*P* interaction
	Q5	Q1	Q5	Q1	Q5	Q1	
Vitamin A							<0.001
Female non-smokers	2096	2564	105	242	ref	1.19 (0.92,1.53)	
Female smokers	109	264	16	53	3.44 (1.86,6.34)	2.00 (1.34,2.99)	
Male non-smokers	394	225	53	47	3.29 (2.26,4.78)	3.20 (2.14,4.78)	
Male smokers	1630	1176	320	444	4.11 (3.10,5.44)¶	5.42 (4.09,7.18)¶	
Carotene							
Female non-smokers	2118	2529	108	226	ref	1.11 (0.86, 1.43)	<0.001
Female smokers	104	268	15	49	3.12 (1.66, 5.85)	1.82 (1.21, 2.74)	
Male non-smokers	397	243	55	50	3.42 (2.36, 4.94)	3.24 (2.19, 4.79)	
Male smokers	1610	1189	321	425	4.51 (3.41, 5.98)	5.27 (3.98, 6.98)	
Vitamin C							
Female non-smokers	2303	2466	112	465	ref	1.04 (0.81,1.35)	<0.001
Female smokers	107	294	12	35	2.23 (1.15,4.32)	1.87 (1.26, 2.78)	
Male non-smokers	401	191	55	55	3.33 (2.31,4.80)	3.24 (2.08, 5.03)	
Male smokers	1419	1278	317	204	4.77 (3.62,6.30)¶	5.61 (4.26, 7.39)¶	

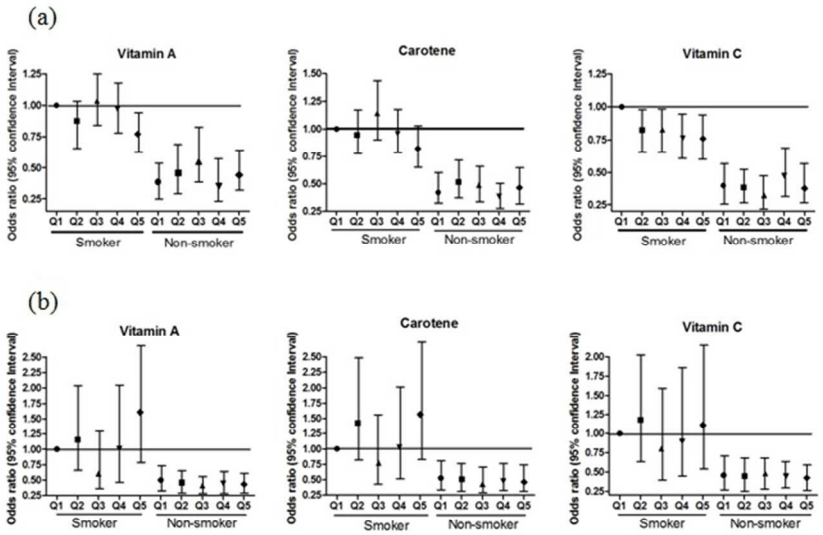
OR (Odd ratio) was determined following adjustment for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level.

¶, The risk for COPD was significantly different between Q1 and Q5.

Table 4. Mean values of adjusted forced expiratory volume in 1-second (FEV_1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.

	Q1	Q2	Q3	Q4	Q5	Difference between 5 and 1 (95% CI)	*P* value for trend	*P* value for interaction
Vitamin A								
COPD	1990	1999	2035	2056	2030	40 (-18,99)	0.126	0.069
Male smokers	2213	2218	2304	2303	2279	66 (-13,145)	0.024	
Male non-smokers	2334	2254	2242	2375	2280	−54 (-262,154)	0.672	
Female smokers	1639	1562	1501	1459	1628	−11(-271, 249)	0.599	
Female non-smokers	1589	1659	1565	1656	1649	60 (-38,158)	0.169	
Carotene								
COPD	1993	2022	2043	2055	2042	49 (-9,108)	0.195	0.044
Male smokers	2211	2250	2296	2317	2276	65 (-13,144)	0.046	
Male non-smokers	2329	2255	2230	2357	2341	12 (-188, 213)	0.665	
Female smokers	1689	1545	1435	1428	1626	−63 (-325,198)	0.094	
Female non-smokers	1573	1649	1628	1600	1657	84 (-14,183)	0.299	
Vitamin C								
COPD	2025	2042	2087	2090	2087	62 (5,120)	0.056	0.179
Male smokers	2235	2278	2330	2314	2336	101(25, 178)	0.039	
Male non-smokers	2402	2256	2330	2459	2256	−146 (-370,78)	0.138	
Female smokers	1603	1600	1630	1597	1563	−40 (-318,239)	0.997	
Female non-smokers	1594	1595	1618	1632	1687	93 (-11,198)	0.433	

Adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, household income, and education level. *P* values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.



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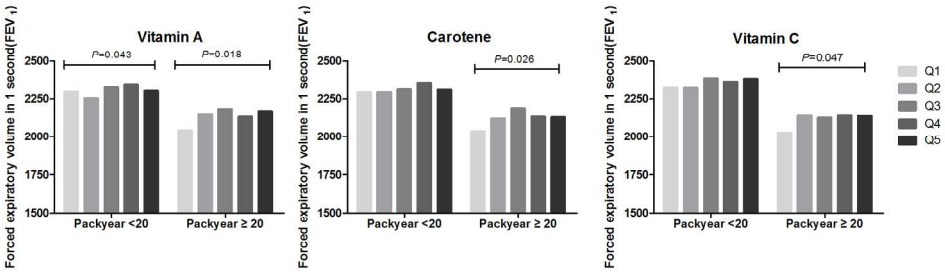

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BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020656.R1
Article Type:	Research
Date Submitted by the Author:	16-Jan-2018
Complete List of Authors:	Hong, Ji Young; Chuncheon Sacred Heart Hospital, Lee, Chang Youl; Chuncheon Sacred Heart Hospital, Hallym University Medical Center, Division of Pulmonary and Critical Care Medicine, Department of Medicine Lee, Myung Goo; Chuncheon Sacred Heart Hospital, Hallym University Medical Center, Division of Pulmonary and Critical Care Medicine, Department of Medicine Kim, Young Sam; Yonsei University College of Medicine
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	lung function, gender, smoking, antioxidant vitamins

Effects of dietary antioxidant vitamins on lung functions according to gender and smoking status in Korea: A population-based cross-sectional study

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Abstract

Objective: Cigarette smoke-induced oxidative stress plays an important role in the pathogenesis of chronic obstructive pulmonary disease (COPD). Dietary antioxidants are thought to prevent smoke-induced oxidative damage. The aim of this study was to investigate associations between lung function and the consumption of antioxidant vitamins in Korean adults.

Methods: In total, 21,148 participants from the Korean National Health and Nutrition Examination Survey (2007–2014) were divided into four groups based on smoking history and gender. Multivariate regression models were used to evaluate associations between lung function and intake of dietary antioxidants.

Results: Subjects in the highest-intake quintile (Q5) of vitamin A, carotene, and vitamin C intake had mean forced expiratory volume in 1 second (FEV_1) measurements that were 30 ml, 32 ml, and 36 ml higher than those of individuals in the lowest-intake quintile (Q1), respectively (*P* for trend; *P*=0.008, *P*=0.010, and *P*<0.001, respectively). The risks of COPD for male smokers in Q1 increased 7.60-fold (95% CI=5.92–9.76), 7.16-fold (95% CI=5.58–9.19), and 7.79-fold (95% CI=6.12-9.92), for vitamin A, carotene, and vitamin C, respectively, compared to those of female non-smokers in Q5. Among COPD patients, males who smoked >20 pack years had mean FEV_1 measurements that were 192 ml, 149 ml, and 177 ml higher than those of patients in Q1 (*P* for trend; *P*=0.018, *P*=0.024, and *P*=0.043, for vitamin A, carotene, and vitamin C, respectively).

Conclusions: These findings indicate that the influence of antioxidant vitamins on lung function depends on gender and smoking status in the Korean COPD population.

Keywords: lung function, gender, smoking, antioxidant vitamins

Strengths and limitation of this study

- This study revealed that the influence of antioxidant vitamins on lung function depends on gender and smoking status in Korean patients with COPD.
- A cross-sectional study with a large sample size collected from a national health survey
- Main limitations include a possible recall bias and no further verification of nutritional intake.

Introduction

Chronic obstructive pulmonary disease (COPD) causes morbidity and mortality[1]. Smoking is a primary risk factor for COPD; however, other factors also contribute as only 10–20% of smokers develop airflow limitations[2].

Dietary antioxidants protect against oxidative stress caused by smoking[3], and multiple studies have revealed associations between the intake of antioxidant vitamins or fibers and respiratory diseases[4-8]. However, evidence supporting the benefits of vitamin supplement therapy is lacking[9 10].

Because micronutrient status is affected by dietary intake and metabolic turnover, which are regulated by oxidative stress, the benefits of antioxidant vitamins may vary by gender and smoking status. Multiple studies have shown that different antioxidants exhibit different effects based on smoking status. Morabia *et al*. reported an association between airway obstruction and vitamin A intake in smokers compared to former smokers, whereas Hu *et al*. reported that carotene was less strongly associated with FEV_1 in smokers compared to former smokers and non-smokers[11 12].

This study used KNHANES data to investigate whether dietary antioxidant vitamins were independently associated with pulmonary function and COPD in the Korean population. This study also evaluated whether the effects of antioxidant vitamins on pulmonary function differed based on gender or smoking status.

Patients and Methods

Study population

Participants were sampled from Korean National Health and Nutritional Examination Survey (KNHANES; 2007–2014) IV–VI, a nationwide survey designed to be representative of the population that is used to establish health policies. KNHANES contains a massive database with information about demographic characteristics, comorbidities, lung function, nutritional status, and health (https://knhanes.cdc.go.kr/knhanes).

A two-stage stratified systemic sampling method was use to select 65,973 individuals to survey between February 2007 and December 2014. Of the chosen individuals, 34,278 participants over 40 years of age responded to questionnaires regarding diet and smoking history and underwent a medical examination. After excluding subjects who omitted lung function or nutrition data, we analyzed data from 21,148 (8,804 men and 12,344 women) in this study. This study was approved by the Institutional Review Board of the Korean Centers for Disease Control and Prevention. All participants provided informed written consent.

Protocol

KNHANES collects survey data through health questionnaire surveys, screening surveys, and nutrition surveys. Health questionnaires were divided into household survey, health interview survey, and health behavior survey. The health interview survey examined the use of medical services, activity limitations, education and economic activities, and physical activity by interview method. The health behavior survey examined smoking status, drinking, mental health, and safety consciousness by self - filling method. The screening consisted of physical measurement, blood pressure and pulse

measurement, blood and urine test, oral examination, pulmonary function test, visual and refractive examination, color vision test, hearing test, and muscle strength test. Nutrition surveys consisted of dietary behaviors, dietary supplements, nutritional knowledge, and the contents of food intake (24-hour recall method) a day before the survey.

Spirometry and airflow obstruction definitions

The pulmonary function test (PFT) was performed using dry-rolling seal volume spirometers (Model 2130; Sensor Medics, Yorba Linda, CA, USA) and standardized according to the American Thoracic Society/European Respiratory Society criteria[13]. Qualified technicians and principal investigators assessed the spirometry data for acceptability and reproducibility. The predictive equations for the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) were derived from survey data on non-smokers who had normal chest X-rays and no previous history of respiratory diseases[14]. COPD was defined as a $FEV_1/FVC < 70\ \%$[15].

Dietary assessments

Food intake data were obtained using the 24-h recall method, in which participants were asked to report the foods and amounts thereof consumed during the previous 24 hours. Total energy (kJ/d (kcal/d)) and total intake of antioxidant vitamins were calculated using the Korean Food Composition Table[16] as the reference. Antioxidant vitamin consumption was adjusted for total energy intake.

Potential confounders

Data regarding demographic information, education level, household income, smoking status, smoking amount, alcohol intake, place of residence, body mass index (BMI), and comorbid diseases were obtained. Educational level was categorized as elementary school or lower, completion of middle school, completion of high school, and college or higher. Household income was divided by quartile. Place of residence was divided to rural and urban.

Smokers were subjects who smoked more than 100 cigarettes in their lifetime[17]. Participants were categorized in terms of smoking status as follows: smoker, ex-smoker, or never smoked. Those who answered in the negative to the question 'Do you currently smoke?' were defined as ex-smokers.

The smoking amount was determined in pack years, which was calculated by multiplying the duration of smoking (years) by the number of packs of cigarettes smoked. Comorbid diseases included hypertension, stroke, cardiovascular disease, arthritis, tuberculosis, asthma, diabetes mellitus, thyroid disorders, renal failure, liver disease, and malignancy.

Statistical analysis

A total of 21,148 subjects participated in this study (Figure 1). The relationship between antioxidant vitamin intake and lung function was analyzed using multiple linear regression analyses. We analyzed the energy-adjusted antioxidant vitamin intake by quintiles. The adjustment factors were age, sex, BMI, educational level, household income, total energy intake, place of residence, number of comorbid diseases, smoking history, alcohol intake, and pack years[4 11 18]. Assessments of linear trends across increasing antioxidant vitamin quintiles were also performed.

We estimated the odds ratios (ORs) of COPD using multivariate logistic regression analyses of quintiles after adjusting for confounding factors. Participants were divided into four groups based on gender and smoking status (male smokers, male non-smokers, female smokers, female non-smokers), to determine whether the relationship between COPD risk and antioxidant vitamin intake is related to gender and smoking status. For combined analyses between the effects of antioxidant vitamin intake, gender, and smoking status on the risk of COPD, interaction tests were performed. COPD patients and male COPD patients were analyzed separately. We attempted to determine whether the association of antioxidant vitamins and lung function varies with gender and smoking status in patients with COPD. Multiple linear regression analyses were performed after categorizing COPD patients by smoking

status and amount.

Statistical analyses were performed using PASW Statistics ver. 20 (SPSS Inc., Chicago IL, USA) and SAS ver. 9.4 (SAS Institute, Cary, NC, USA) software. *P*-values <0.05 were considered statistically significant.

Results

The baseline characteristics of the 21,148 participants are shown in Table 1. All subjects were classified into four groups based on smoking history and gender. Of the 7,986 smokers, 7,178 were male (mean age, 57.8±11.0 years) and 808 were female (mean age, 57.4±12.5 years). Of the 13,162 individuals who had never smoked, 1,626 were male (mean age, 57.9±11.3 years) and 11,536 were female (mean age, 57.1±10.8 years). Among all subjects, 3,005 were diagnosed with COPD. The prevalence of COPD was highest in male smokers (26.4%) and lowest in female non-smokers (6.4%).

The four groups differed regarding age, BMI, educational level, household income, and alcohol usage (P<0.001). Energy intake was significantly higher in males than females (males, 2,256.5 kcal; females, 1,648.3 kcal; P<0.001). The levels of vitamin A, carotene, and vitamin C were highest in the male non-smoker group and lowest in the female smoker group. Korean male non-smokers are pre-disposed to COPD compared to female non-smokers (incidence rate of 15.7% versus 6.4%). Age and the percentage of alcohol intake were higher in Korean male non-smokers than female non-smokers.

Table 2 showed the association between lung function (FEV_1, FVC) and dietary antioxidant vitamin levels. Participants in the highest quintile (Q5) of vitamin A intake had 30 ml higher FEV_1 (P for trend across quintiles = 0.008) and 33 ml higher FVC (P for trend across quintiles = 0.007) compared to participants in the lowest quintile (Q1). Participants in Q5 for carotene intake had 32 ml higher FEV_1 (P for trend across quintiles = 0.010) and 36 ml higher FVC (P for trend across quintiles = 0.005) measurements compared to participants in Q1. Participants in Q5 of vitamin C intake had 36 ml higher FEV_1 (P for trend across quintiles <0.001) and 35 ml higher FVC (P for trend across quintiles = 0.014) measurements compared to participants in Q1. A statistically significant dose–response relationship was observed (all, P for trend across quintiles <0.005), but participants in Q3 of vitamin A and carotene had comparable lung function to those in Q5.

The effects of gender, smoking, and dietary antioxidant vitamins on the risk of COPD are summarized in Table 3. The risk of COPD for male smokers in Q1 for vitamin A, carotene, and vitamin C intake increased by 7.60-fold (95% CI=5.92–9.76), 7.16-fold (95% CI=5.58–9.19), and 7.79-fold (95% CI=6.12-9.92), respectively, which was greater than that observed for female non-smokers in Q5 for antioxidant vitamin intake. Interestingly, the risk of COPD for male non-smokers in Q5 for vitamin A, carotene, and vitamin C intake increased by 3.26-fold (95% CI=2.24-4.75). 3.35-fold (95% CI=2.31-4.86) and 3.28-fold (95% CI=2.27-4.73), respectively, compared with female non-smokers in Q5 for antioxidant vitamin intake. The risk of COPD for male non-smokers in Q1 for vitamin A, carotene, and vitamin C intake increased by 2.80-fold (95% CI=1.90-4.12). 3.25-fold (95% CI=2.21-4.78) and 3.17-fold (95% CI=2.04-4.91), respectively, compared with female non-smokers in Q1 for antioxidant vitamin intake. These results suggest that men may have other causes of COPD as well as smoking, compared with women who took similar amounts of antioxidant vitamins.

The interaction exists between the antioxidant vitamin intake and gender/smoking status on the risk of COPD (all *P*-values <0.001). The effect of the antioxidant vitamin intake depends on the gender/smoking status. When assessing the risk of COPD following reduction of antioxidant intake from Q5 to Q1, only male smokers showed significant difference in risk of COPD, but other three groups did not. Figure 2 shows that the risk of COPD was influenced by dietary antioxidant vitamin levels in male smokers, in detail. In male smokers, the risk of COPD in subjects in Q5 for antioxidant vitamins intake was significantly lower than that for subjects in Q1 (vitamin A, OR = 0.77, 95% CI = 0.63–0.94, P = 0.009; carotene, OR = 0.81, 95% CI = 0.67–0.99, P=0.041; vitamin C, OR = 0.74, 95% CI = 0.61–0.91, P = 0.004). The dose –dependent effect of vitamin C was observed between COPD risk and dietary antioxidant vitamin levels, but it was not for vitamin A and carotene. Although not significant, Q3 group of carotene had increased risk to develop COPD than Q1 group of carotene.

The prevalence of COPD did not increase significantly as the intake of dietary antioxidant vitamins

increased in male non-smokers, female smokers, or female non-smokers. No significant interaction between the effects of antioxidant vitamins on COPD and smoking status was observed. The correlation between the risk of COPD and antioxidant vitamin intake was stronger in male smokers who smoked less than 20 pack years (not shown).

We investigated the association between dietary antioxidant vitamin intake and lung function after limiting the analyses to individuals with COPD. The changes in FEV_1 were not statistically significant based on the levels of dietary antioxidant vitamins in subjects with COPD. Similar to the previous results, only male smokers in subjects with COPD, exhibited a beneficial association between dietary antioxidant vitamin intake and FEV_1 (Figure 3). Male smokers with COPD in Q5 for vitamin A intake had a 71-ml higher FEV_1 (*P* for trend across quintiles = 0.019) compared to those in Q1. Male smokers with COPD in Q5 of carotene and vitamin C intake had 71-ml higher FEV_1 (*P* for trend across quintiles = 0.037) and a 109-ml higher FEV_1 (*P* for trend across quintiles = 0.026), respectively, compared to individuals in Q1.

Additional analyzes were performed to determine if lung function was reduced by smoking amount or smoking status in male smoker- COPD patients. Male COPD patients who had smoked ≥20 pack years exhibited a beneficial association between dietary antioxidant vitamin intake and FEV_1 (Figure 4). Male COPD patients in Q5 of vitamin A intake who had smoked ≥ 20 pack years had a 192-ml higher FEV_1 (*P* for trend across quintiles = 0.018) compared to individuals in Q1. COPD patients in Q5 of carotene intake who had smoked ≥20 pack years had a 149-ml higher FEV_1 (*P* for trend across quintiles = 0.024) compared with patients in Q1. COPD patients in Q5 of vitamin C intake who had smoked >20 pack years had a 177-ml higher FEV_1 (*P* for trend across quintiles = 0.043) compared to patients in Q1.

Discussion

This study examined the association between the intake of antioxidant vitamins and lung functions in the Korean population. Previous studies showed that antioxidant vitamins, including vitamin C, were protective of the human lung [5 12], whereas high levels of vitamin A and carotene were also associated with increased lung functions in multiple studies[11 19-23]. In a randomized controlled trial, Keranis *et al*. reported that increasing the intake of antioxidants improved lung function[24].

Cigarette smoking is the primary cause of COPD as it increases oxidative stress in the lungs and activates inflammatory responses[25]. Notably, one inhalation from a cigarette generates more than 10^{15} free radicals and other oxidants[26].

Antioxidants protect against the damage caused by smoking in multiple ways[3]. For example, as it is water-soluble, vitamin C scavenges free radicals in the cytoplasm. Koike *et al*. reported that vitamin C diminished smoke-induced oxidative stress and corrected emphysematous lungs *in vivo*[27].

Carotenoids quench singlet oxygen and inhibit lipid peroxidation[3]. In an animal study, the respiratory epithelia of retinol-deficient animals had atrophied ciliated cells and modified lipid contents[28]. The pathologic features of the retinol-deficient animals were similar to those of human smokers[29].

Smokers exhibit nicotine-induced reductions in intestinal absorption and elevated metabolic turnover[30]. The metabolism or destruction of antioxidant vitamins increases in inflammatory environments[31-34], which suggests that smokers with COPD require larger amounts of antioxidant vitamins to achieve the same blood levels as non-smokers. A study by Sargeant found that vitamin C may modify the adverse effects of smoking and the risk of COPD in the European population[35]. Additionally, Shin *et al.* reported that Korean smokers with adequate vitamin C intake had acceptable pulmonary functions[36] and Park et al showed that dietary vitamin C provides protection against

COPD[37]. Additionally, Morabia *et al.* identified that airway obstruction was reduced by vitamin A in smokers[11].

One notable finding in the current study was that the effects of antioxidant vitamin intake on lung function were stronger among male smokers. Additionally, the association between the risk of COPD and antioxidant vitamin intake was clear for male but not female smokers. Male smokers with lower antioxidant vitamin intakes had increased ORs of COPD compared to female smokers. Although the dose-dependent effect on COPD risk was not obvious in vitamin A and carotene, contrary to vitamin C (Figure 2), male smokers with Q5 intake showed a clearly reduced risk to develop COPD than male smokers with Q1 intake in all three antioxidant vitamins.

After limiting the analysis to subjects with COPD, a significant association between antioxidant vitamin intake and FEV_1 was observed in male smokers but not in other groups. This finding was similar to that of Joshi *et al.,* where changes in COPD risk and dietary vitamin C and vitamin E intake differed between males and females [38].

It is not known how gender differences impact pulmonary functions based on antioxidant vitamin intake; however, animal studies have revealed gender differences in antioxidant vitamin requirements. Al Rejaie *et al.* reported gender-related differences in the protective roles of ascorbic acid against oxidative stress[39], whereas Jiao *et al*. revealed gender differences in the regulation and expression of oxidative genes in mice [40].

Studies detailing the effects of antioxidant vitamins on lung function in smokers and non-smokers are lacking [5 23]. In the US population, Britton *et al.* revealed that the relationship between vitamin C intake and FEV_1 was stronger in ex-smokers than non- or current smokers[5]. Shahar *et al*. reported a relationship between individuals in Q1 of vitamin A intake and airway obstruction among individuals who smoked >41 pack years [23].

Among male COPD patients, those smoking ≥20 pack years had improved lung functions as antioxidant vitamin intake increased. These results support that associations between antioxidants and lung function may differ according to smoking status in COPD patients. However, it is unknown what causes such differences. One hypothesis is that the efficacy of antioxidant vitamins is proportional to the level of oxidant burden in COPD. Additional studies are required to determine whether the benefits of antioxidant vitamins depend on the smoking duration or dose in COPD patients.

This study has several limitations that should be noted. As we used a cross-sectional design, the data cannot be used to answer questions regarding causation. Additionally, because data on nutritional intake were obtained by 24-hour recall, inaccurate responses may have been offered. This study used the pre-bronchodilator FEV_1 for determining COPD; however, the definition of COPD is based on post-bronchodilator FEV_1[15]. This study failed to obtain data regarding air pollution or occupational exposure and, therefore, could not associate these variables with lung function; however, the strength of this study is that these data represent the Korean population.

Conclusion

This study supports that antioxidant vitamins have beneficial effects on pulmonary function in the Korean population. The data indicate that there is a stronger association between antioxidant vitamin intake and the risk of COPD in male smokers. The beneficial effects of antioxidant vitamins in COPD patients differed by gender and smoking status, and future investigations should determine the roles of dietary antioxidant vitamins in specific groups.

Contributors

JYH and YSK equally contributed to the conception and design of the research; YSK contributed to the design of the research; CYL contributed to the acquisition and analysis of the data; MGL and

YSK contributed to the interpretation of the data; and JYH drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding

This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) & funded by the Korean government (MSIT) (NRF-2017M3A9E8033225). This work was supported by the National Research Foundation of Korea Grant funded by Korean Government (NRF 2017R1C1B5017879).

Competing interests

None declared

Provenance and peer review

Not commissioned; externally peer reviewed

Data sharing statement

No additional data are available.

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Table legends

Table 1. Study population characteristics.

¶, numbers represent mean percentages (standard deviation).

Table 2. Mean values of adjusted lung function measurements across quintiles of vitamin A, carotene, and vitamin C intake.

Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, smoking history, pack years (smoking amount), household income, and education level.

P values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.

Table 3. Association between vitamin A, carotene, and vitamin C intake and COPD according to gender and smoking status.

OR was determined following adjustment for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, household income, and education level.

¶, The risk for COPD was significantly different between Q1 and Q5.

Table 1. Study population characteristics

	Total (n=21,148)	Male smokers (n=7,178)	Male non-smokers (n=1.626)	Female smokers (n=808)	Female non-smokers (n=11,536)	*P* value
Age ¶	57.4 (10.9)	57.8 (11.0)	57.9 (11.3)	57.4 (12.5)	57.1 (10.8)	<0.001
40–49	6048 (28.6)	1998 (27.8)	464 (28.5)	273 (33.8)	3313 (28.7)	<0.001
50–59	6131 (29.0)	1981 (27.6)	431 (26.5)	199 (24.6)	3520 (30.5)	
60–69	5387 (25.5)	1913 (26.7)	430 (26.4)	158 (19.6)	2866 (25.0)	
70–	3582 (16.9)	1286 (17.9)	301 (18.5)	178 (22.0)	1817 (15.8)	
BMI¶	24.2 (3.0)	24.2 (2.8)	24.3 (2.8)	23.8 (3.6)	24.2 (3.2)	0.007
Education						<0.001
Elementary	7229 (34.2)	1763 (24.6)	321 (19.7)	381 (47.2)	4764 (41.3)	
Middle school	3315 (15.7)	1216 (16.9)	267 (16.4)	112 (13.9)	1720 (14.9)	
High school	6427 (30.4)	2366 (33.0)	458 (28.2)	228 (28.2)	3375 (29.3)	
More than college	4169 (19.7)	1831 (25.5)	580 (35.7)	87 (10.8)	1671 (14.5)	
Household income						<0.001
1st quartile	4763 (22.5)	1440 (20.1)	289 (17.8)	315 (39.0)	2719 (23.6)	
2nd quartile	5427 (25.7)	1874 (26.1)	391 (24.1)	223 (27.6)	2939 (25.5)	
3rd quartile	5162 (24.4)	1869 (26.1)	414 (25.5)	145 (17.9)	2734 (23.7)	
4th quartile	5780 (27.3)	1988 (27.7)	530 (32.6)	125 (15.5)	3137 (27.2)	
Comorbidity¶	0.9 (1.1)	0.9 (1.0)	0.8 (0.9)	1.0 (1.2)	1.0 (1.1)	<0.001
Pack years¶	4.7 (13.6)	13.3 (20.3)	0.2 (2.2)	3.3 (11.9)	0.0 (0.0)	<0.001
Alcohol	17554 (83.0)	6877 (95.8)	1399 (86.0)	714 (88.4)	8564 (74.2)	<0.001
Energy intake (Kcal/day)¶	1901.5 (797.8)	2266.5 (869.7)	2212.6 (855.9)	1538.2 (653.4)	1656.0 (630.0)	<0.001
Vitamin A (μg RE/day)¶	822.5 (1118.5)	881.9 (1067.5)	925.5 (1095.2)	600.3 (644.2)	786.6 (1173.9)	<0.001
Carotene (μg/day)¶	4337.3 (6206.0)	4596.2 (5557.8)	4803.8 (5506.6)	3143.5 (3682.6)	4194.1(6780.6)	<0.001
Vitamin C (mg/day)¶	111.9 (107.6)	111.8 (97.9)	128.8 (107.1)	84.8 (96.9)	111.5 (113.5)	<0.001
FEV_1 (ml)¶	2.60 (0.67)	3.02 (0.68)	3.09 (0.66)	2.23 (0.56)	2.30 (0.46)	<0.001
FVC (ml)¶	3.38 (0.84)	4.07 (0.72)	4.04 (0.73)	2.88 (0.62)	2.89 (0.51)	<0.001
FEV1/FVC (%)¶	77.3 (7.9)	73.9 (9.1)	76.6 (7.9)	77.2 (8.0)	79.5 (6.1)	<0.001
COPD	3,005 (14.2)	1893 (26.4)	256 (15.7)	119 (14.7)	737 (6.4)	<0.001

¶, numbers represent mean percentages (standard deviation).

Table 2. Mean values of adjusted lung function measurements across quintiles of vitamin A, carotene, and vitamin C intake.

	Q1	Q2	Q3	Q4	Q5	Difference between Q5 and Q1 (95% CI)	*P* value for trend
Vitamin A							
Mean intake (μg RE)	151.2	353.6	573.1	893.9	2140.8		
FEV_1 (ml)	2379	2389	2410	2397	2409	30 (10,50)	0.008
FVC(ml)	3119	3136	3158	3148	3152	33 (10,57)	0.007
Predicted FEV_1 (%)	91.37	91.44	91.91	91.45	91.94	0.57 (-0.08,1.22)	0.185
Predicted FVC (%)	90.93	91.06	91.45	91.22	91.48	0.55 (0.00,1.10)	0.195
Carotene							
Mean intake (μg)	691.1	1747.4	2938.9	4736.1	11574.1		
FEV_1 (ml)	2347	2363	2376	2370	2379	32 (12,52)	0.010
FVC (ml)	3088	3117	3127	3119	3124	36(13.59)	0.005
Predicted FEV_1 (%)	91.55	92.03	92.26	91.85	92.31	0.76 (0.12,1.39)	0.096
Predicted FVC (%)	91.02	91.68	91.78	91.41	91.82	0.80 (0.26,1.33)	0.015
Vitamin C							
Mean intake (mg)	24.2	53.6	84.2	128.8	268.9		
FEV_1 (ml)	2411	2423	2436	2441	2453	36 (16.56)	<0.001
FVC (ml)	3117	3122	3132	3140	3154	35 (12.58)	0.014
Predicted FEV_1 (%)	91.3	91.5	91.9	91.99	92.21	0.91 (0.27,1.55)	0.050
Predicted FVC (%)	91.29	91.33	91.58	91.77	92.0	0.71 (0.17,1.26)	0.118

Data were adjusted for age, sex, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence smoking history, pack years (smoking amount), household income, and education level. *P* values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.

Table 3. Association between vitamin A, carotene, and vitamin C intake and COPD according to gender and smoking status.

	Intake		COPD		OR		*P* interaction
	Q5	Q1	Q5	Q1	Q5	Q1	
Vitamin A							<0.001
Female non-smokers	2096	2564	105	242	ref	1.16 (0.89,1.49)	
Female smokers	109	264	16	53	3.90 (2.12,7.17)	2.42 (1.63, 3.58)	
Male non-smokers	394	225	53	47	3.26 (2.24,4.75)	3.15 (2.10,4.72)	
Male smokers	1630	1176	320	444	5.54 (4.28,7.16)¶	7.60 (5.92, 9.76)¶	
Carotene							
Female non-smokers	2118	2529	108	226	ref	1.10 (0.85,1.42)	<0.001
Female smokers	104	268	15	49	3.47 (1.86,6.47)	2.16 (1.45, 3.23)	
Male non-smokers	397	243	55	50	3.35 (2.31,4.86)	3.24 (2.18,4.82)	
Male smokers	1610	1189	321	425	5.83 (4.51,7.53)¶	7.16 (5.58, 9.19)¶	
Vitamin C							
Female non-smokers	2303	2466	112	465	ref	1.00 (0.77,1.30)	<0.001
Female smokers	107	294	12	35	2.37 (1.20,4.71)	2.27 (1.55, 3.34)	
Male non-smokers	401	191	55	55	3.28 (2.27,4.73)	3.24 (2.07, 5.06)	
Male smokers	1419	1278	317	204	6.20 (4.82,7.98)¶	7.79 (6.12, 9.92)¶	

OR (Odd ratio) was determined following adjustment for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, household income, and education level.

¶, The risk for COPD was significantly different between Q1 and Q5.

Figure Legends

Figure 1. The study population framework

Figure 2. Odds ratios for the association between antioxidant vitamin intake and COPD among (a) male and (b) female smokers and non-smokers.

Odds ratios were adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, household income, and education level.

Figure 3. Mean values of adjusted forced expiratory volume in 1-second (FEV_1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.

Adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, household income, and education level. *P* values were determined using tests for linear trends across increasing quintiles (means) of antioxidant vitamin intake.

Figure 4. Mean values of adjusted forced expiratory volume in 1-second (FEV_1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD patients according to smoking status.

Values were adjusted for age, body mass index, energy intake, number of comorbid diseases, alcohol consumption, place of residence, household income, and education level. *P*-values were determined using tests for linear trends across increasing quintiles (median) of antioxidant vitamin intake.

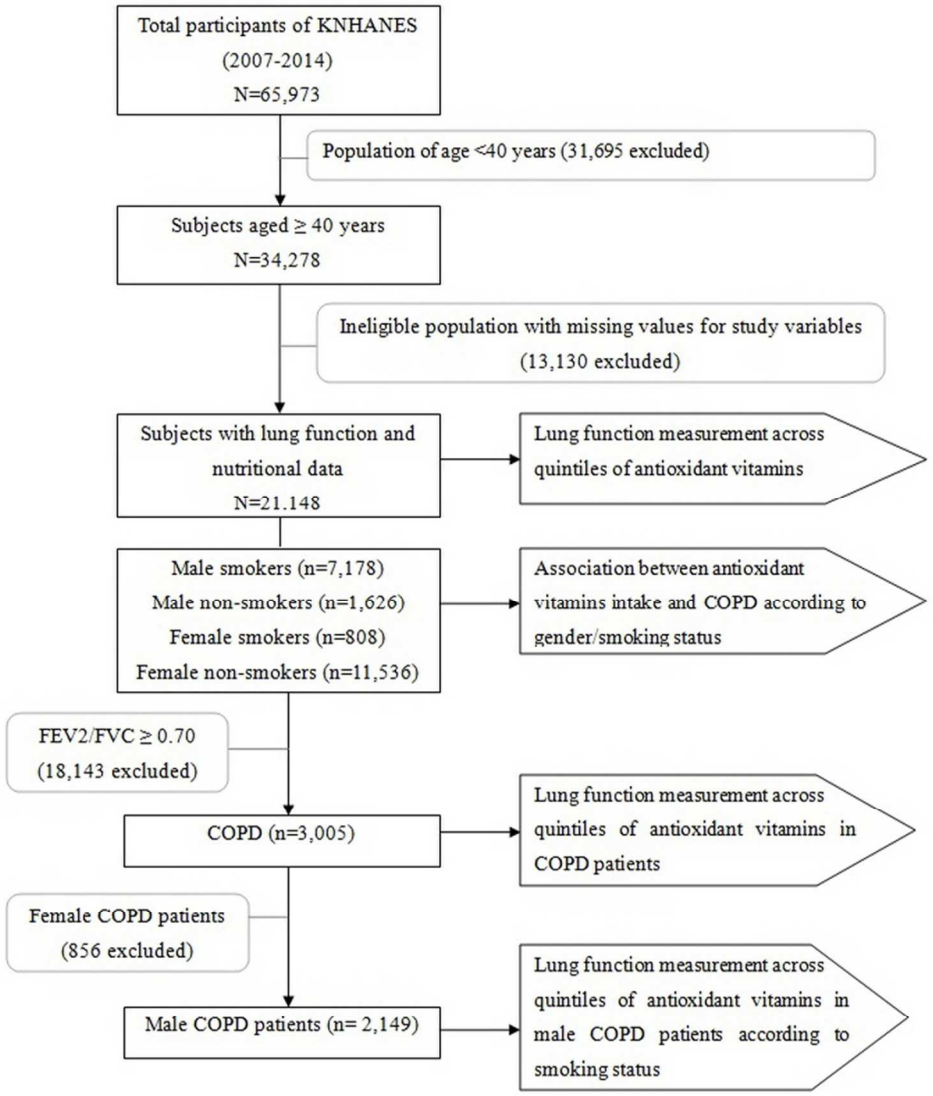

Figure 1. The study population framework

240x274mm (300 x 300 DPI)

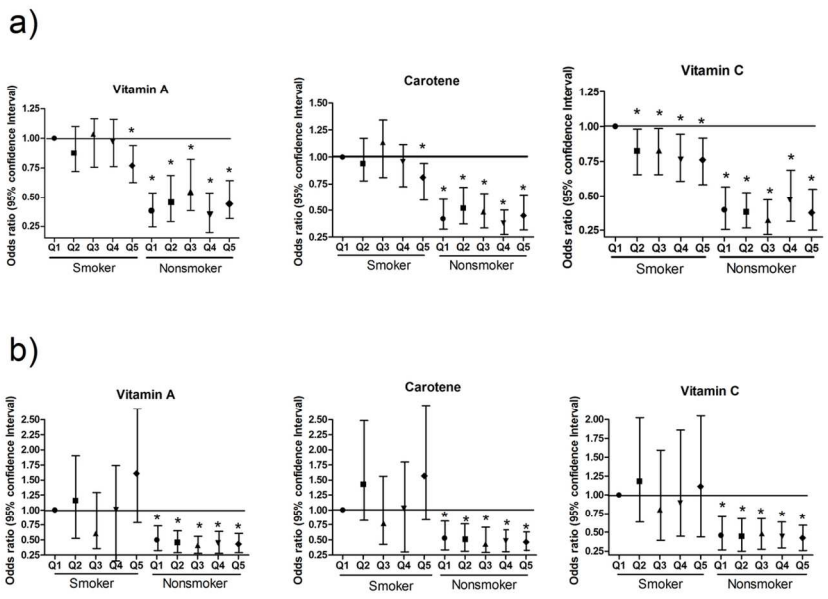

Figure 2. Odds ratios for the association between antioxidant vitamin intake and COPD among (a) male and (b) female smokers and non-smokers

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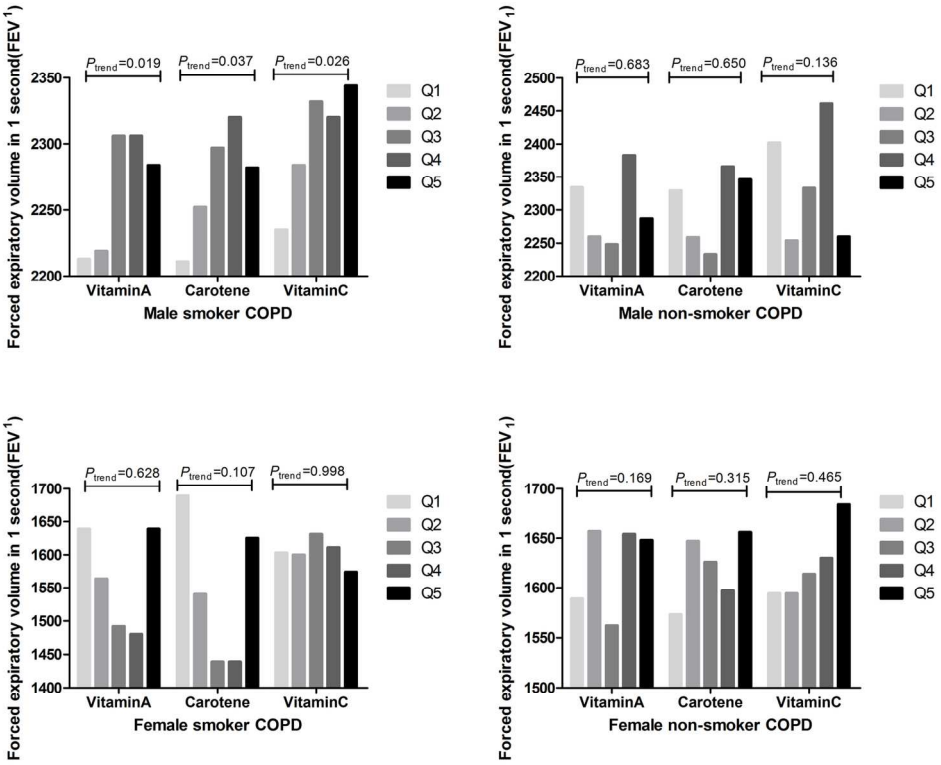

Figure 3. Mean values of adjusted forced expiratory volume in 1-second (FEV1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in subjects with COPD.

148x121mm (300 x 300 DPI)

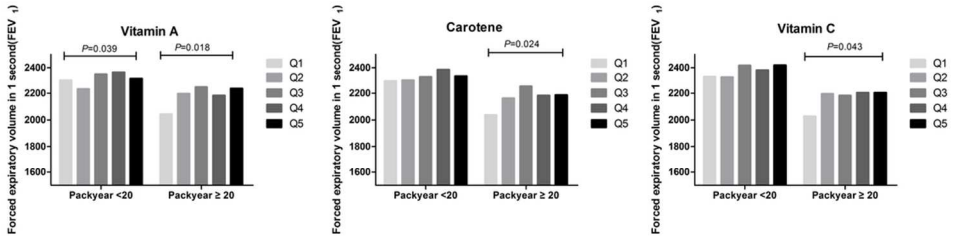

Figure 4. Mean values of adjusted forced expiratory volume in 1-second (FEV1) measurements across quintiles of vitamin A, carotene, and vitamin C intake (energy-adjusted) in male COPD patients according to smoking status.

50x14mm (600 x 600 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	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	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(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	9
		(b) Give reasons for non-participation at each stage	Figure1
		(c) Consider use of a flow diagram	Figure1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	10-11
Main results	16	(*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	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	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	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Impact of serious game design elements on engagement and educational outcomes of healthcare professionals and students: a systematic review and meta-analysis protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019871
Article Type:	Protocol
Date Submitted by the Author:	03-Oct-2017
Complete List of Authors:	Maheu-Cadotte, Marc-André; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Cossette, Sylvie ; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Dubé, Veronique; Université de Montréal, Faculty of Nursing; Centre de recherche du CHUM Fontaine, Guillaume; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Mailhot, Tanya; Université de Montréal, Faculty of Nursing; Institut De Cardiologie de Montreal, Research Center Balli, Fabio; Condordia University Mathieu-Dupuis, Gabrielle; Université de Montréal, School of Librarianship and Information Science
Keywords:	Information technology < BIOTECHNOLOGY & BIOINFORMATICS, MEDICAL EDUCATION & TRAINING, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

Impact of serious game design elements on engagement and educational outcomes of healthcare professionals and students: a systematic review and meta-analysis protocol.

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Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Abstract

Introduction: Serious games (SGs) are interactive digital software with a primary educational purpose that engage the learner by proposing a challenge. The effectiveness of SGs in healthcare professionals' and students' education was underlined as mixed in recent reviews. This could be explained by design elements (DEs) in SGs which have been found to be highly variable across studies. Therefore, the aim of this systematic review is to identify, appraise, and synthesize the best available evidence regarding the impact of DEs in SGs on engagement and educational outcomes of healthcare professionals and students.

Methods and analysis: We will conduct a systematic search of the literature with the assistance of a librarian. We will use a combination of MeSH terms and keywords to search relevant bibliographical databases. We will include studies comparatively assessing on engagement, learning, and behavior change at least two SGs with at least one DE variation. We will conduct the title, abstract and full text screening process with the assistance of at least two independent reviewers. We will assess the risk of bias of included studies using the Effective Practice and Organisation of Care (EPOC) criteria. Data regarding DEs in SGs will first be synthesized qualitatively. Depending on the availability and quality of data, we will perform a meta-analysis. We will assess the quality of the evidence regarding the impact of each DE on each outcome by using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach.

Ethics and dissemination: As this systematic review only uses already collected data, no Institutional Review Board approval is required. We plan to submit the results in a peer-reviewed journal by the end of 2018.

Systematic review registration: PROSPERO International Prospective Register of Systematic Reviews #XXXXXX

Strengths and limitations of the review

- A comprehensive and prospectively registered (PROSPERO #XXXXX) systematic literature review protocol reported according to the Preferred

Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.

- An assessment of the overall quality of the evidence according to each design element in serious games and each selected outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.
- The definition given to the concept of “serious game” in this systematic review is hindered by the fact that no consensus prevails in the literature.

Introduction

Healthcare professionals' and students' education is of primarily importance to assure the adoption of best practices and to improve patients' safety. The World Health Organization underlined in 2013 the need to train healthcare professionals who are able to face population health needs and the reality of health service delivery [1]. Engagement, defined as the learner's involvement and interest towards the educational intervention, has been positively correlated numerous times with educational outcomes such as learning and behavior change [2 3]. Designing educational interventions able to sustain healthcare professionals' and students' engagement is therefore critical to their effectiveness. As such, the last decade has seen a growing interest from researchers about the use of serious games (SGs) in healthcare professionals' and students' education [4].

Serious games are designed as active learning environments which can be available on any digital platform (e.g. smartphone, computer). Learning typically occurs in SGs by offering a gameplay that engages the learner to gradually face challenges adapted to his in-game skills development. Challenges are defined as subjective experiences where the learner feels that his skills are summoned in order to achieve [5]. Challenges can require from the learner to explore, experiment, compete, or cooperate with other learners [6 7]. The gameplay is defined by a combination of these challenges and by various design elements (DEs) [8]. These DEs, which can be seen as building blocks (e.g. points, unlockable content, rewards for achievement) [9], are suggested to be instrumental in improving learner's engagement [4 10]. Design elements operate by influencing antecedents of engagement such as: a clear challenge to be achieved, the learner's ability to focus, his sense of control, and the feedback he receives. Consequently, these DEs make for gameplay which will hinder or aid the learner's engagement and, therefore, educational outcomes [11 12].

However, previous reviews in healthcare professionals and students have underlined the mixed effectiveness of SGs when compared to other educational interventions (e.g. classroom learning) in either improving engagement or educational outcomes [4 13 14]. As previous authors pointed out, the integration of the educational aim

to the gameplay is a delicate process that should be considered throughout SGs development, right up to the designing phase [15 16]. As such, it is suggested that the mixed effectiveness of SGs in supporting engagement and improving educational outcomes could be explained by the highly variable DEs found in SGs [17]. Moreover, recent theoretical papers about SG development reported that the optimal integration of DEs has yet to be found [15 18]. As the development of SGs can be quite expensive and time-consuming [19], identifying the impact of DEs on engagement and educational outcomes could inform the efficient development of future SGs [13]. Previous systematic reviews were able to quantify the impact of several DEs in simulation (e.g. range of task difficulty, repetitive practice) [20 21] and internet-based education (e.g. integration of an online discussion forum and audio files) [22] by adopting a similar approach to the one we propose. However, to our knowledge, a systematic review in the domain of SGs assessing the impact of DEs on engagement and educational outcomes of healthcare professionals and students has yet to be published.

Primary objective

To systematically identify, appraise, and synthesize the best available evidence regarding the impact of DEs in SGs on engagement and educational outcomes of healthcare professionals and students.

Methods

The protocol for this systematic review was developed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) [23] (see supplementary file 1). The protocol was also registered prospectively on the PROSPERO International Prospective Register of Systematic Reviews (# XXXXXXX).

Eligibility criteria

We will state on the eligibility of studies based on study characteristics, participants, interventions assessed, comparators, and the outcome measures.

Study characteristics

We will consider primary studies published in English or in French from 2005 to 2017. Previous reviews in SGs have identified a growth in published literature starting mid-2000's [17 24] and no experimental study assessing a SG for healthcare professionals' and students' education before that time point [4].

Types of participants

We will consider studies conducted with healthcare professionals and students from all levels of education (from undergraduate to postgraduate education) either in a clinical (continuing education) or an academic setting. Clinicals settings include all environments in which healthcare is provided.

Types of interventions

We will consider studies assessing a SG as a standalone intervention; studies assessing a combination of a SG with another educational intervention (e.g. workshop, classroom or digital-based learning) will not be considered. For this systematic review, we define SGs as interactive digital software with a primary educational purpose that engage the learner through various challenges [5 8 25 26].

Types of comparators

We will consider studies with at least two groups receiving each a SG that varies for at least one DE between groups (see Table 1 for the complete list of DEs to be assessed). If no such study is identified, we will consider studies where the comparator is any other type of educational intervention.

Types of outcome measures

We will consider studies reporting measures of engagement and educational outcomes.

We will retain the definition and the indicators of engagement reported by Perski et al. [3] . These authors define engagement as two-dimensional: 1) the extent of the

learner's involvement; and 2) a subjective experience characterised by affect, attention and interest. We will considerer individually these two dimensions. Regarding learner's involvement, we will look at both the duration and the frequency of SGs usage, either self-reported or electronically measured by the SGs. Regarding the learner's subjective experience, we will consider self-reported measures (e.g. acceptability? questionnaire).

We will define the educational outcomes, which are learning and behavior change, according to the levels of evaluation proposed by Kirkpatrick [27]. Learning represents the knowledge that was acquired (e.g. factual knowledge), the skills that were improved (e.g. how to perform a certain procedure), or the attitudes that were changed (e.g. how worthwhile the learner believes it is to apply the learning in his day-to-day role) after playing the SG. We will considerer individually these three dimensions (i.e. knowledge, skills, and attitude). Behavior change represents a change in the day-to-day role of the healthcare professionals or the students after playing the SG. For this review, we will both consider reporting of subjective (e.g. self-reported evaluation) and objective measures (e.g. quiz) of learning and behavior change.

Information sources

Bibliographical databases

We will identify eligible primary studies through a comprehensive search of six bibliographical databases: Cumulative Index of Nursing and Allied Health (EBSCO), EMBASE (OVID), ERIC (ProQuest), PsycINFO (APA PsycNET), PubMed (NCBI), and Web of Science – SCI and SSCI (ISI – Thomson Scientific).

Hand searching

We will hand-search relevant journals for additional articles. Such journals include, but are not limited to: *Games, G|A|M|E The Italian Journal of Game Studies, International Journal of Computer Games Technology, International Journal of Serious Games,* and *JMIR Serious Games.* We will also hand-search for additional articles the reference lists of identified studies and previous systematic reviews related to the educational use of serious games.

Search strategy for bibliographical databases

We collaboratively and iteratively developed the search strategy with the assistance of a librarian. We initially developed the search strategy for PubMed using a combination of medical subject headings (MeSH) and keyword related to the following key concepts: serious games, healthcare professionals/ healthcare students, and effect on educational outcomes. The search strategy was then translated for the other bibliographical databases (see supplementary file 2).

Study records

Data management

We will import and manage all collected references in EndNote (Version X8, Clarivate Analytics). Based on the eligibility criteria, we will manage and categorize references in specific files and sub-files inside the software. We will make available reference in the software and upload the full-texts after the selection process.

Selection process

Three reviewers will independently perform the selection process of the collected references. We will first screen the titles and the abstracts by applying the previously stated eligibility criteria. We will then perform a full-text assessment of the remaining references. We will resolve all disagreements through discussion and consensus. We will document the reasons for excluding references and report them in a PRISMA flow diagram [28].

Data extraction process

Two independent reviewers will independently perform the data extraction process using an adapted electronic format of the Effective Practice and Organisation of Care (EPOC) data extraction template. The original template was developed by the EPOC editorial team to serve as a guide in extracting data from primary studies [29]. Notwithstanding data regarding the studies' eligibility, we will extract data regarding the DEs of the SGs assessed the results according to the previously stated outcomes. We

will also extract data needed to assess the risk of bias (e.g. allocation concealment, blinding). All data items to be collected are further listed. We will contact corresponding authors in the case of unclear or missing data in the published articles. We will then enter all data in RevMan (Version 5.3, The Cochrane Collaboration) a software which allows data management and analysis during the process of a systematic review and a meta-analysis [30].

Data items

To guide the extraction of data items related to DEs, we'll refer to DEs presented in Table 1 and identified following a literature search by the review authors [9 31-33]. Additional elements relevant to evaluating the impact of SGs and to be investigated in this review are also presented in Table 1. These additional elements were chosen based on the additional burden they could place on the cost and the time needed to develop SGs [34]. Accordingly, we will extract the following data items from the included studies:

- The population and the setting: study population, setting, and inclusion and exclusion criteria.
- The methods: study aim, design employed, unit of allocation, study's start and end dates, duration of participation, unit of measurement, time points measured, tools used to measure the outcome and, tools' validity.
- Participants: sample size, baseline characteristics and imbalances between groups, age, sex, education level, number of years of practice as a health professional (or level and year of education, if a student), clinical or academic setting.
- Intervention (SG): SGs' name, theoretical framework used for the development, cost and duration of development, clinical topic addressed, DEs (see Table 1), frequency of SGs use, duration of SGs use, time spent between the first and the last SGs use.
- Outcomes: engagement, knowledge, skill, attitude, and behavior change.

Assessment of risk of bias

Two authors will independently assess and justify the risk of bias of included studies using the EPOC standard risk of bias criteria [35]. Nine criteria are used and, for each one of them, the study can be judged at "low risk", "high risk", or "unclear risk" of bias. A high risk of bias diminishes the reliability of the study's results. The criteria account for aspects regarding the allocation sequence and concealment, measurements and characteristics of baseline outcome, incomplete outcome data, selective outcome reporting, contamination, blinding, and other risk of bias. Specific guidance to evaluate the risk of bias individually for each criterium is provided by EPOC. Each criterium will be considered independently and no attempt at assigning an overall score at each study will be made, as suggested by EPOC [35]. We will resolve all disagreements about the risk of bias assessment of the two authors through discussion and, if needed, with the help of a third review author.

Assessment of selective reporting of outcomes

We will assess the selective reporting of outcomes by comparing the outcomes reported in the primary study with the ones stated in the published research protocol. If no published research protocol is available, we will look if the study was prospectively registered and compare the outcomes reported in the primary study with the ones in the registration form. If the study was not prospectively registered, we will compare the outcomes presented in the method section with the ones reported in the result section. In all cases, the corresponding authors of studies for which there are discrepancies in the outcomes reported will be contacted by e-mail to obtain relevant unreported data.

Assessment of publication bias

If more than 10 studies are included in the meta-analysis, we will assess publication bias by constructing a funnel plot with RevMan (Version 5.3, The Cochrane Collaboration) [30]. The interpretation of the funnel plot will follow the guidance included in the Cochrane handbook for systematic reviews [36].

Data synthesis

Quantitative data synthesis

The meta-analysis will evaluate the impact of each DE on engagement, knowledge acquisition, skill development, and attitude and behavior change. We will pool in a meta-analysis studies assessing head-to-head comparisons of a SG that varies for at least one DE between groups (e.g. we will pool all the studies where the DE assessed was the presence or not of a leaderboard). If a study has more than one DE varying between the groups, then this study will part of multiple group analysis (e.g. one study could be part of the "Leaderboard" group analysis and the "Story" group analysis).

Because we anticipate moderate heterogeneity [24], we will use random-effects models to pool weighted effect sizes. We will calculate pooled weighted effect sizes with 95% confidence interval for each SG design element and for each outcome. We will determine the significance of the effect sizes using Cohen's classification (<0.2=negligible; 0.2– 0.49=small; 0.5–0.8=moderate; >0.8=large) [37]. We will define a statistically significant result by a two-sided alpha of 0.05. We will perform all quantitative data synthesis using RevMan (Version 5.3, The Cochrane Collaboration) [30].

Assessment of heterogeneity

Statistical heterogeneity represents the inconsistency of the studies' results and the percentage of variation across studies that is not due to chance [38]. We will assess statistical heterogeneity using the Chi² test and the I^2 statistic within RevMan (Version 5.3, The Cochrane Collaboration) [30]. We will considerer a I^2 value superior to 50% as a high level of heterogeneity.

Sensitivity analysis

We will perform sensitivity analysis to evaluate if the exclusion of studies at high risk of bias would affect the findings of the meta-analysis and the statistical heterogeneity for each previously stated outcome. If we are unable to explain heterogeneity this way, the synthesis of results will be exclusively narrative.

Subgroup analysis

If sufficient data is available, we will try to explain the source of heterogeneity by exploring clinical and methodological diversity. Therefore, we will conduct subgroup analyses according to the following criteria:

1. **Population:** Whether current healthcare professionals or students are the focus of the study.
2. **Publication year:** Whether the study was published before or after 2014. As SG development is intrinsically linked to the technological state at a given moment, it is suggested that the overall quality of SGs should have improved in the last couple of years, thus their effectiveness on supporting engagement and improving educational outcomes [24]. In parallel, the New Media Consortium declared in 2014 that the use of SGs was to be significantly experimented by educational institutions in the next two to three years [39].

Assessment of the overall quality of evidence

We will assess the quality of the evidence regarding each DE and each outcome by using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach [40]. GRADE formalizes the process of evaluating the overall quality of evidence and formulating recommendations. For each individual outcome, there are four levels of quality of evidence (very low, low, moderate, high) which represent our confidence in the estimate of effect. Quality of evidence depends on factors such as risk of bias, unexplained heterogeneity, and indirectness of the evidence. Two authors will independently assess and justify the quality of evidence regarding the impact of DE on each selected outcome. We will resolve all disagreements through discussion and, if needed, with the help of a third review author.

Qualitative data synthesis

We will provide a qualitative data synthesis whether a meta-analysis will have been performed or not. We will present descriptive data (e.g. year published, country of origin, population, sample size, study design, name of the SG assessed, clinical topic addressed, outcomes measured) of each included study in a tabular form. We will also present a summary table containing an overview of all DE included in the SGs

assessed. We will present narratively the results according to the DE and their impact on engagement and educational outcomes.

Ethics and dissemination

As this systematic review only use already collected data, no ethics approval is required. The review is currently registered (PROSPERO # XXXX). We plan to submit the results in a peer-reviewed journal by the end of 2018.

Discussion

This systematic review will fulfill important needs in the designing of SGs for healthcare professionals' and students' education. As previous systematic reviews focused on evaluating the overall effectiveness of SGs in the healthcare professions [4 14 41 42], to the best of our knowledge, this will be the first systematic review to assess the impact of DEs in SGs on engagement and educational outcomes. Also, by describing which DEs have been integrated in the designing of SGs, this systematic review will facilitate the identification of gaps that will guide the development of future SGs. Furthermore, a thorough reporting of the risk of bias in studies assessing SGs in the healthcare professions has yet to be published. Therefore, the use of the EPOC standard risk of bias criteria [35] will assist in describing the overall quality of the current evidences.

Moreover, depending on the homogeneity of the data and the overall quality of included studies, the planned meta-analysis, will provide valuable information about the expected effect size associated with various DEs. Here again, to the best of our knowledge, a meta-analysis pursuing this aim has yet to be published.

The protocol of this systematic review is prospectively registered (PROSPERO #XXXX) and is reported according to the PRISMA-P guidelines [23]. Our research strategy was collaboratively designed with the assistance of a librarian and will extensively cover several relevant databases. However, as clear criteria have yet to be established in the literature regarding what can be considered a SG, we will adopt an inclusive definition that does not discriminate based on the SG type [5 8 25 26]. In the case of ambiguity regarding the inclusion of specific studies due to the nature of the of intervention, review

authors will assess their eligibility through discussion and consensus. Nonetheless, this limitation will be addressed in the reporting of the full systematic review and considered in the formulation of recommendations.

Authors' contributions

All authors contributed to the conception of the protocol. MAMC wrote the initial draft of the protocol. SC, VD, GF, TM, FB, and GMD critically revised the initial draft for important intellectual content. All authors gave final approval of the manuscript submitted.

All authors agreed to be accountable for all aspects related to this work.

Acknowledgements

This research was carried out as part of the doctoral studies of the first author and for which he received scholarships from the followings: Montreal Heart Institute Foundation, Ministère de l'Éducation et de l'Enseignement supérieur du Québec, Faculty of Nursing of the Université de Montréal, and the Fondation J.A. DeSève.

Data sharing

No additional data available.

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Table 1. Design elements in serious games and additional elements to be assessed

Design elements	
Avatars	The learner chooses or creates a graphical representation to represent himself in the serious game.
Badges for achievement	A visual representation that serves as a symbol for the learner's achievements.
Content unlocking	Access to new aspects of the serious game (e.g. higher levels) when certain tasks have been accomplished.
Difficulty adaptation	Difficulty level of challenges can user-adjusted (e.g. easy, medium, and hard) or automatically adjusted to the learner's performance.
Hints	A suggestion or an indication given by the serious game to help the learner achieve a challenge. A learner can choose himself to receive a hint or the serious game can give it to him based on his performance.
Leaderboard	A table or a graph that ranks the learners according to their success based on specific criteria.
Performance tables or graphs	A table or a graph that provide information to the learner about the progression of his performance over time.
Points	Points are awarded or subtracted depending on the learner's performance and serve to numerically represent the progression. Points can therefore serve as a reward and as an immediate feedback tool.
Story	A narrative context that serves to contextualise and give meanings to the challenges to be achieved.
Teams	Learners who work together to achieve a common goal. Teams will be broadly

	regarded here to encompass either cooperative or versus playing.
Time pressure	A time limit that is allowed for the learner to achieve a specific challenge. Time pressure can be illustrated by a countdown timer that indicates to the learner the time remaining.
Virtual goods	Game assets that have a certain in-game value. Virtual goods can sometimes be bought or exchanged using real-world currency.
Additional elements	
Graphics	Whether the graphics of the serious game was presented in two or three dimensions.
Method of delivery	The platform on which the serious game is played (e.g. smartphone, computer, videogame console).

Supplementary file 1 – PRISMA-P Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	94-95
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	385-292
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	393-397
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	106-149
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	150-153
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	159-202
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	203-215
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	216-222 Supplementary file 2
STUDY RECORDS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	224-228
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	229-235
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	236-248
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	249-269
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	183-202
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	270-282
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	299-305

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	306-312
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	313-336
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	348-355
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	283-296
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	337-347

Supplementary file 2 – PubMed search strategy

1. serious gam*[TIAB] OR applied gam*[TIAB] OR ((simulation[TIAB] OR training[TIAB] OR
teaching[TIAB] OR educational[TIAB] OR education[TIAB] OR learning[TIAB] OR
interactive[TIAB]) AND (((online[TIAB] OR electronic[TIAB] OR digital[TIAB] OR "over-thecounter"[
TIAB] OR commercial[TIAB] OR computer[TIAB] OR virtual[TIAB] OR mobile
application*[TIAB] OR mobile app[TIAB]) AND (game[TIAB] OR games[TIAB] OR
gamification[TIAB] OR gaming[TIAB] OR)) OR (videogame*[TIAB] OR video game*[TIAB]))
2. "Video Games"[MH]
3. #1 OR #2
4. Health Personnel*[TIAB] OR Health professional*[TIAB] OR Health care profession*[TIAB] OR
Healthcare profession*[TIAB] OR Medical student*[TIAB] OR Medical assistant*[TIAB] OR
health worker*[TIAB] OR Audiologist*[TIAB] OR Chiropractor*[TIAB] OR Dentist[TIAB] OR
Dentists[TIAB] OR Dietitian*[TIAB] OR Dermatolog*[TIAB] OR endocrinologist*[TIAB] OR
Gastroenterolog*[TIAB] OR Gynecolog*[TIAB]OR Radiolog*[TIAB] OR Medical Staff[TIAB]
OR Midwife*[TIAB] OR neurologi*[TIAB] OR nutritionist*[TIAB] OR Nurse[TIAB] OR
Nurses[TIAB] OR nursing[TIAB] OR Optometrist*[TIAB] OR Occupational Therapist*[TIAB]
OR Patholog*[TIAB] OR Paramedic[TIAB] OR Paediatric[TIAB] OR pediatrician*[TIAB] OR
Paediatrician*[TIAB] OR pediatrist*[TIAB] OR pediatric[TIAB] OR Pharmacist*[TIAB] OR
Pharmaconomist*[TIAB] OR Pharmacologist*[TIAB] OR Pharmacy technician*[TIAB] OR
Phlebotomist*[TIAB] OR Physician OR Podiatrist*[TIAB] OR Psychologist*[TIAB] OR
Psychotherapist*[TIAB] OR psychiatrist*[TIAB] OR Physical therapist*[TIAB] OR
physiotherapist*[TIAB] OR Respiratory therapist*[TIAB] OR Surgeon*[TIAB] OR surgical
[TIAB] OR Clinician*[TIAB] OR Cardiologist*[TIAB] OR medical technician*[TIAB] OR
emergency doctor*[TIAB] OR emergentologist*[TIAB] OR clinical officer*[TIAB] OR
Community health worker*[TIAB] OR Radiographer*[TIAB] OR Radiotherapist*[TIAB] OR
technologist[TIAB] OR Anesthetist*[TIAB] OR Resident[TIAB] OR residents[TIAB] OR
trainee[TIAB] OR trainees[TIAB] OR intern[TIAB] OR interns[TIAB]
5. "Health Personnel"[MH] OR "Students, Premedical"[MH] OR "Students, Medical"[MH] OR
"Students, Nursing"[Mesh]
6. "Education, Premedical"[MH] OR "Education, Medical"[MH] OR "Education, Nursing"[MH] OR
"Education, Pharmacy"[MH] OR "Education, Public Health Professional"[MH] OR "Clinical
Clerkship"[MH]

7. #4 OR #5 OR 6
8. knowledge*[TIAB] OR aptitude*[TIAB] OR accuracy[TIAB] OR ability[TIAB] OR abilities[TIAB] OR capacity [TIAB] OR capacities[TIAB] OR confidence[TIAB] OR competency[TIAB] OR competencies[TIAB] OR impact*[TIAB] OR skill*[TIAB] OR performance*[TIAB] OR learning outcome*[TIAB] OR training outcome*[TIAB] OR effectiveness[TIAB] OR efficacy[TIAB] OR improvement*[TIAB] OR innovative*[TIAB] OR innovation*[TIAB] OR retention[TIAB] OR randomised controlled trial[TIAB] OR randomized
controlled trial[TIAB]
9. "Clinical Competence"[MH] "Quality Improvement"[MH] OR "Learning Curve"[MH] OR
Knowledge [MH] OR "Educational Measurement"[MH] OR "randomized controlled trial"[PT]
10. #8 OR 9
11. #3 AND #7 AND #10
12. (english[LA] OR french[LA]) AND 2000:2017[DP]
13. #11 AND #12

BMJ Open

Effectiveness of serious games and impact of design elements on engagement and educational outcomes in healthcare professionals and students: a systematic review and meta-analysis protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019871.R1
Article Type:	Protocol
Date Submitted by the Author:	14-Dec-2017
Complete List of Authors:	Maheu-Cadotte, Marc-André; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Cossette, Sylvie ; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Dubé, Veronique; Université de Montréal, Faculty of Nursing; Centre de recherche du CHUM Fontaine, Guillaume; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Mailhot, Tanya; Université de Montréal, Faculty of Nursing; Institut De Cardiologie de Montreal, Research Center Lavoie, Patrick; Boston College - William F Connell School of Nursing Cournoyer, Alexis; Universite de Montreal Faculte de medecine; Hopital du Sacre-Coeur de Montreal Balli, Fabio; Condordia University Mathieu-Dupuis, Gabrielle; Université de Montréal, School of Librarianship and Information Science
Primary Subject Heading:	Medical education and training
Secondary Subject Heading:	Health informatics
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, MEDICAL EDUCATION & TRAINING, Information technology < BIOTECHNOLOGY & BIOINFORMATICS

Effectiveness of serious games and impact of design elements on engagement and educational outcomes in healthcare professionals and students: a systematic review and meta-analysis protocol.

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Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Abstract

Introduction: Serious games (SGs) are interactive digital software with an educational purpose. They engage the learner by proposing challenges and through various design elements (DEs; e.g. points, difficulty adaptation, story). Recent reviews suggest the effectiveness of SGs in healthcare professionals' and students' education is mixed. This could be explained by the variability in their DEs, which has been shown to be highly variable across studies. The aim of this systematic review is to identify, appraise, and synthesize the best available evidence regarding the effectiveness of SGs and the impact of DEs on engagement and educational outcomes of healthcare professionals and students.

Methods and analysis: A systematic search of the literature will be conducted using a combination of MeSH terms and keywords in CINAHL, EMBASE, ERIC, PsycInFO, PubMed, and Web of Science. Studies assessing SGs on engagement and educational outcomes will be included. Two independent reviewers will conduct the screening as well as the data extraction process. The risk of bias of included studies will also be assessed by two reviewers using the Effective Practice and Organisation of Care (EPOC) criteria. Data regarding DEs in SGs will first be synthesized qualitatively. A meta-analysis will then be performed, if the data allows it. Finally, the quality of the evidence regarding the effectiveness of SGs on each outcome will be assessed using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach.

Ethics and dissemination: As this systematic review only uses already collected data, no Institutional Review Board approval is required. Its results will be submitted in a peer-reviewed journal by the end of 2018.

Systematic review registration: PROSPERO International Prospective Register of Systematic Reviews # CRD42017077424

Strengths and limitations of the review

- A comprehensive and prospectively registered (PROSPERO #CRD42017077424) systematic literature review protocol reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.
- An assessment of the overall quality of the evidence regarding effectiveness of SGs on each outcome, using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach
- The definition of "serious game" in this systematic review is limited by the fact that no consensus prevails in the literature.

Introduction

Education of healthcare professionals and students is of the utmost importance to promote the adoption of best practices and to improve patient safety. In 2013, the World Health Organization underlined a need to train healthcare professionals to face population health needs and health service delivery adapted to epidemiological and demographic realities.[1] Engagement, defined as a learner's involvement and interest towards an educational intervention, has been positively correlated with educational outcomes such as learning and behavior change.[2 3] Designing educational interventions to sustain the engagement of healthcare professionals and students is therefore critical to their effectiveness. As such, the last decade has seen a growing interest from researchers about the use of serious games (SGs) in healthcare professionals' and students' education.[4]

Serious games are designed as active learning environments which can be made available on any digital platform (e.g. smartphone, computer). Learning in SGs typically occurs through a gameplay that engages the learner in challenges adapted to his in-game skills. Challenges are defined as subjective experiences that solicit the learners' skills.[5] For example, challenges can require the learner to explore, experiment, compete, or cooperate with other learners.[6 7] Gameplay is defined as a combination of challenges and design elements (DEs).[8]

Design elements (DEs), which can be seen as building blocks or shared features of games (e.g. points, difficulty adaptation, story), are suggested to be instrumental in improving the learner's engagement in SGs.[4 9 10] Therefore, a SG may be composed of several DEs and these DEs may be similar across SGs.[11] A list of DEs, based on a literature review by the authors, is presented in Table 1.[10 12-14] Based on Csikszentmihalyi's flow theory and theoretical propositions of other authors in game design, Pavlas suggests that DEs operate by influencing antecedents of engagement such as: the learner's ability to concentrate on task, his sense of control, the feedback he receives, and a deep but effortless involvement.[15] As Lameras et al. underlines the difficulty in linking DEs and engagement to specific learning processes in SGs, it is believed that higher engagement will lead the learner to become deeply involved and to repeatedly take on the challenges offered to improve his in-game performance, and, consequently, his educational outcomes.[16] However, while supporting engagement, there are also concerns that DEs can

become a source of distraction from the learning content and negatively affect educational outcomes.[15 17 18]

Previous reviews have highlighted the mixed effectiveness of SGs when compared to other educational interventions (e.g. classroom learning) in improving healthcare professionals' and students' engagement or educational outcomes.[4 19 20] As previous authors pointed out, the integration of an educational purpose to the gameplay is a delicate process that should be considered throughout SGs development, right up to the initial designing phase of the SGs.[21 22] As such, the mixed effectiveness of SGs in supporting engagement and improving educational outcomes could be explained by the highly variable DEs found in SGs.[23] Moreover, the optimal integration of DEs in SGs remains to be discovered.[21 24] Findings from a recent meta-analysis investigating the effectiveness of SGs on healthy lifestyle promotion underlined the necessity of strong theoretical foundations in designing SGs and the need to further explore which DEs are the most impactful.[25] As the development of SGs can be quite expensive and time-consuming, describing which DEs have been integrated in the development of SGs for healthcare professionals and students, as well as their impact on engagement and educational outcomes, could help in the efficient development of future SGs.[19 26] However, a systematic review of the impact of DEs of SGs on engagement and educational outcomes has yet to be published.

Therefore, our objectives are two-fold: 1) To systematically identify, appraise, and synthesize the best available evidence regarding the effectiveness of SGs on engagement and educational outcomes of healthcare professionals and students; and 2) To describe which DEs have been integrated in the development of SGs for healthcare professionals and students, and their impact on engagement and educational outcomes.

Methods

The protocol for this systematic review was developed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P; see supplementary file 1) and follows the guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions.[27 28] The protocol was also registered prospectively on the PROSPERO International Prospective Register of Systematic Reviews (# CRD42017077424).

Eligibility criteria

The eligibility of studies will be assessed based on study characteristics, participants, interventions assessed, comparators, and the outcome measures for inclusion in the systematic review and the meta-analysis.

Study characteristics

Primary studies published in English or in French from January 1st 2005 to December 31th 2017 will be considered. Previous reviews on SGs have identified a growth in published literature starting mid-2000's[23 29]; and no experimental study assessing an SG for healthcare professionals' and students' education was found before that date.[4] As suggested Effective Practice and Organisation of Care (EPOC) Cochrane Review Group, randomised controlled trials and cluster randomised controlled trials will be included in the current review.[30]

Types of participants

Studies with healthcare professionals and healthcare students from undergraduate to postgraduate education, either in a clinical or an academic setting will be considered. Clinical settings include all environments in which healthcare is provided. Studies conducted exclusively among patients or students receiving non-healthcare related education (e.g. high school students) are beyond the scope of this review as the objectives of the games evaluated in these populations (e.g. illness self-management in patients, the learning of mathematical concepts in students) differ from those developed for healthcare professionals and healthcare students.

Types of interventions

Studies assessing a SG as a stand-alone intervention, or as part of multi-component intervention (e.g. combined with workshop, classroom or digital-based learning) will be considered. For this systematic review, we define SGs as interactive digital software with a primary educational purpose that engage a learner through various challenges.[5 8 31 32]

Types of comparators

We will consider studies where the comparator is any type of educational intervention.

Types of outcome measures

Studies reporting at least one measure of engagement or educational outcomes will be considered.

We will retain the definition and the indicators of engagement reported by Perski et al., who defined engagement as: 1) the extent of a learner's involvement; and 2) a subjective experience characterised by affect, attention, and interest.[3] These two dimensions will be considered individually. For involvement, we will look at both the duration and the frequency of SGs usage, either self-reported or electronically measured by the SGs. For subjective experience, we will consider self-reported measures.

We will define the educational outcomes, which are learning and behavior change, according to the levels of evaluation proposed by Kirkpatrick.[33] Learning represents the knowledge that was acquired (i.e. factual knowledge; e.g. knowledge about the physiopathology of a specific disease), the skills that were improved (i.e. how to perform a certain procedure; e.g. ultrasound needle placement), or the attitudes that were changed (i.e. how worthwhile the learner believes it is to apply the learning in his day-to-day role; e.g. attitudes towards pain management) after playing the SG. These three dimensions will be considered separately (i.e. knowledge, skills, and attitude). Behavior change represents a change in the day-to-day role of the healthcare professionals or the students after playing the SG (e.g. coronary heart disease patients' referral to cardiac rehabilitation by healthcare professionals). For this review, we will consider studies reporting both subjective (e.g. self-reported evaluation) and objective measures (e.g. quiz) of learning and behavior change.

Information sources

Bibliographical databases

Eligible primary studies will be identified through a comprehensive search of six bibliographical databases: Cumulative Index of Nursing and Allied Health (EBSCO), EMBASE (OVID), ERIC (ProQuest), PsycINFO (APA PsycNET), PubMed (NCBI), and Web of Science – SCI and SSCI (ISI – Thomson Scientific).

Hand searching

Relevant journals will be hand-searched for additional articles. Such journals include, but are not limited to: Games for Health Journal, *Games, G|A|M|E The Italian Journal of Game Studies, International Journal of Computer Games Technology, International Journal of Serious Games,* and *JMIR Serious Games*. We will also hand-search for additional articles the reference lists of identified studies and previous systematic reviews related to the use of serious games in healthcare care professionals and healthcare students.

Search strategy for bibliographical databases

The search strategy was collaboratively and iteratively developed with the assistance of a librarian. We initially developed the search strategy for PubMed using a combination of medical subject headings (MeSH) and keyword related to the following key concepts: serious games, healthcare professionals/ healthcare students, and effect on educational outcomes. The search strategy was then translated for the other bibliographical databases (see supplementary file 2).

Study records

Data management

All collected references will be imported and managed in EndNote (Version X8, Clarivate Analytics). Based on the eligibility criteria, we will manage and categorize references in specific files and sub-files inside the software. Full-texts will be uploaded in the software at the corresponding stage of the selection process.

Selection process

Three reviewers will independently perform the selection process of the collected references. The titles and the abstracts will be screened by applying the previously stated eligibility criteria. A full-text assessment of the remaining references will then be performed. We will resolve all disagreements through discussion and consensus. Reasons for excluding references will be documented and reported in a PRISMA flow diagram at the full-text assessment stage of the selection process.[34]

Data extraction process

Two independent reviewers will independently perform the data extraction process using an adapted electronic format of the Effective Practice and Organisation of Care (EPOC) data extraction template. The original template was developed by the EPOC editorial team to serve as a guide in extracting data from primary studies.[35] The reviewers will pilot the form by individually extracting data from a study and by comparing completed forms. Precisions will be added, and wording will be revised, if needed. Notwithstanding data regarding the studies eligibility, we will extract data regarding the DEs of the SGs assessed the results according to the previously stated outcomes. Data needed to assess the risk of bias (e.g. allocation concealment, blinding) will also be extracted. All data items to be collected are listed below. All corresponding authors will be contacted in the case of unclear or missing data in the published articles. We will enter all data in RevMan (Version 5.3, The Cochrane Collaboration), a software which allows data management and analysis during the process of a systematic review and a meta-analysis.[36]

Data items

To guide the extraction of data items related to DEs, a list of DEs was identified through a literature search by the authors (see Table 1).[10 12-14] Accordingly, we will extract the following data items from the included studies:

- The population and the setting: study population, setting, and inclusion and exclusion criteria;
- The methods: study aim, design employed, unit of allocation (e.g. individual, group), the start and end dates of the study, duration of participation, unit of measurement, time points measured, tools used to measure the outcome and, validity of the tools;
- Participants: sample size, baseline characteristics, statistical differences at baseline between groups, age, sex, education level, number of years of practice as a healthcare professional (or level and year of education, if a student), and clinical or academic setting;
- Intervention (SG): name of the SG, theoretical framework used for the development, cost and duration of development, clinical topic addressed, DEs (see Table 1), frequency of SG use and, and duration of SG use;

- Comparator: method of delivery of the comparator intervention (e.g. e-learning, face-to-face), frequency, and duration, clinical topic addressed;
- Outcomes: engagement, knowledge, skill, attitude, and behavior change;
- "Risk of bias" data (as outlined below).

Assessment of risk of bias

Two authors will independently assess the risk of bias of included studies using the EPOC criteria.[37] Nine criteria are used and, for each one of them, the study can be judged at "low risk", "high risk", or "unclear risk" of bias. A high risk of bias diminishes the reliability of the study's results. The criteria account for aspects regarding the allocation sequence and concealment, measurements and characteristics of baseline outcome, incomplete outcome data, selective outcome reporting, contamination, blinding, and other risk of bias. Specific guidance to evaluate the risk of bias individually for each criterion is provided by EPOC. Each criterion will be considered independently and no attempt at assigning an overall score at each study will be made, as suggested by EPOC.[37] We will resolve all disagreements about the risk of bias assessment of the two authors through discussion and, if needed, with the help of a third review author.

Assessment of selective reporting of outcomes

We will assess the selective reporting of outcomes by comparing the outcomes reported in the primary study with the ones stated in the published research protocol. If no published research protocol is available, we will check if the study was prospectively registered and compare the outcomes reported in the primary study with the ones in the registration form. If the study was not prospectively registered, we will compare the outcomes presented in the methods section with the ones reported in the results section. In all cases, the corresponding authors of studies for which there are discrepancies in the outcomes reported will be contacted by e-mail to obtain relevant unreported data.

Assessment of publication bias

If more than 10 studies are included in the meta-analysis, we will assess publication bias by constructing a funnel plot with RevMan (Version 5.3, The Cochrane Collaboration).[36] The

interpretation of the funnel plot will follow the guidance included in the Cochrane handbook for systematic reviews. [27] If not, the assessment of publication bias will be done qualitatively.

Data synthesis

Quantitative data synthesis

The meta-analysis will evaluate the effectiveness of SGs on healthcare professionals and students' engagement and educational outcomes. In the case of serious reporting or publication bias, no meta-analysis will be performed. This decision will be made by consensus between review authors while also considering clinical and methodological diversity.[27]

When multiple trial arms are reported in a single trial, we will include only the relevant arms according to the intervention received and the comparison made (i.e. SG versus any type of educational intervention). If multiple comparisons are relevant in a single study, we will split the "shared" group in multiple subgroups to allow pair-wise comparisons. No minimal number of participants per arm will be required in order for a study to be initially included in the meta-analysis.

Random-effects models will be used to pool weighted effect sizes. It is assumed, by using random-effects models, that intervention effect across studies follow a distribution and are not all giving an estimate of the same intervention effect.[27] The decision to use random-effect models was made due to the expected variability between SGs (notably on DEs). Pooled weighted effect sizes will be calculated with 95% confidence interval for each outcome. Continuous outcomes that were obtained by using different measures will be grouped by using standardised mean differences. The significance of the effect sizes will be determined using Cohen's classification (<0.2=negligible; 0.2–0.49=small; 0.5–0.8=moderate; >0.8=large).[38] We will define a statistically significant result by a two-sided alpha of 0.05. All quantitative data synthesis will be realized using RevMan (Version 5.3, The Cochrane Collaboration).[36]

Assessment of heterogeneity

Statistical heterogeneity represents the inconsistency of the studies' results and the percentage of variation across studies that is not due to chance.[39] We will assess statistical heterogeneity using the Chi^2 test and the I^2 statistic within RevMan (Version 5.3, The Cochrane Collaboration).[36] A I^2 value superior to 50% will be considered as a high level of heterogeneity.

Subgroup analysis

If sufficient data are available, we will try to explain the source of statistical heterogeneity by exploring clinical and methodological diversity. Therefore, subgroup analyses will be conducted according to the following criteria:

1. **Population:** Whether current healthcare professionals or students are the focus of the study.
2. **Intervention:** Whether the serious game was delivered as a stand-alone intervention or as part of a multi-component intervention.
3. **Publication year:** Whether the study was published before or after 2014. As SG development is intrinsically linked to the technological state at a given moment, it is suggested that the overall quality of SGs should have improved in the last couple of years, and similarly their effectiveness in supporting engagement and improving educational outcomes.[29] In parallel, the New Media Consortium declared in 2014 that the use of SGs was to be significantly experimented by educational institutions in the next two to three years.[40]

Sensitivity analyses

Sensitivity analyses will be performed to evaluate if the exclusion of studies at high risk of bias and of small studies would affect the findings of the meta-analysis and the statistical heterogeneity for each previously stated outcome. If, after exclusion of studies at high risk of bias and of small studies (if appropriate), at least three studies included in the meta-analysis evaluated SGs containing a specific DE (see Table 1), we will perform sensitivity analyses to evaluate the impact of this DE on engagement and educational outcomes. This minimal number of studies (3) is necessary to minimize, during analysis, the potential risk of homogeneity in the DEs integrated to the SGs.

Assessment of the overall quality of evidence

The quality of the evidence regarding the overall effectiveness of SGs and each outcome will be assessed by using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach.[41] GRADE formalizes the process of evaluating the overall quality of evidence and formulating recommendations. For each individual outcome, there are four levels of quality of evidence (very low, low, moderate, high) which represent our confidence

in the estimate of effect. Quality of evidence depends on factors such as risk of bias, unexplained heterogeneity, and indirectness of the evidence. Two authors will independently assess and justify the quality of evidence regarding the overall effectiveness of SGs on each selected outcome. All disagreements will be resolved through discussion and consensus.

Qualitative data synthesis

A qualitative data synthesis will be presented whether or not a meta-analysis will have been performed. Descriptive data (e.g. year published, country of origin, population, sample size, study design, name of the SG assessed, clinical topic addressed, outcomes measured) of each included study will be presented in a tabular form. A summary table containing an overview of all DEs included in the SGs assessed will also be presented. The results according the overall effectiveness of SGs, and the impact of DEs on engagement and educational outcomes will be presented narratively.

Ethics and dissemination

As this systematic review only use already collected data, no ethics approval is required. The review is currently registered (PROSPERO #CRD42017077424). We plan to submit the results in a peer-reviewed journal by the end of 2018.

Discussion

This systematic review will fulfill important needs in the designing of SGs for healthcare professionals' and students' education. As previous systematic reviews focused on a narrative evaluation of the overall effectiveness of SGs in the healthcare professions[4 20 42 43], to our knowledge, this will be the first systematic review to describe and evaluate of the impact of the pre-specified DEs on engagement and educational outcomes. Previous systematic reviews were able to quantify the impact of several DEs in simulation (e.g. range of task difficulty, deliberate practice)[44 45] and internet-based education (e.g. integration of an online discussion forum and audio files).[46] Depending on the quantity of data available, planned sensitivity analyses will allow the quantitative evaluation of the impact of the DEs on selected outcomes. However, we acknowledge that possible homogeneity in DEs integrated to SGs could represent a limit to planned sensitivity analysis.

The protocol of this systematic review is prospectively registered (PROSPERO #CRD42017077424) and is reported according to the PRISMA-P guidelines.[28] Our research strategy was collaboratively designed with the assistance of a librarian and will extensively cover several relevant databases. However, as clear criteria have yet to be established in the literature regarding what can be considered a SG, we will adopt an inclusive definition that does not discriminate based on the SG type (e.g. quiz, management).[5 8 31 32] In the case of ambiguity regarding the inclusion of specific studies due to the nature of the of intervention, review authors will assess their eligibility through discussion and consensus. Nonetheless, this limitation will be addressed in the reporting of the full systematic review and considered in the formulation of recommendations. Moreover, as the integration of the selected DEs in SGs developed for healthcare professionals and students is currently unknown, it is currently planned to describe the integration of these DEs in developed SGs and their alignment with theoretical foundations, as stated by the authors.

Authors' contributions

All authors contributed to the conception of the protocol. MAMC wrote the initial draft of the protocol. SC, VD, GF, TM, PL, AC, FB, and GMD critically revised the initial draft for important intellectual content. All authors gave final approval of the manuscript submitted. All authors agreed to be accountable for all aspects related to this work.

Acknowledgements

This research was carried out as part of the doctoral studies of the first author and for which he received scholarships from the followings: Montreal Heart Institute Foundation, Ministère de l'Éducation et de l'Enseignement supérieur du Québec, Faculty of Nursing of the Université de Montréal, Fondation J.A. DeSève, and Fondation Alice-Girard.

Data sharing

No additional data available.

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Table 1. Design elements in serious games to be assessed

Design elements	
Avatars	The learner chooses or creates a graphical representation to represent himself in the serious game.
Badges for achievement	A visual representation that serves as a symbol for the learner's achievements.
Content unlocking	Access to new aspects of the serious game (e.g. higher levels) when certain tasks have been accomplished.
Difficulty adaptation	Difficulty level of challenges can user-adjusted (e.g. easy, medium, and hard) or automatically adjusted to the learner's performance.
Hints	A suggestion or an indication given by the serious game to help the learner achieve a challenge. A learner can choose himself to receive a hint or the serious game can give it to him based on his performance.
Leaderboard	A table or a graph that ranks the learners according to their success based on specific criteria.
Performance tables or graphs	A table or a graph that provide information to the learner about the progression of his performance over time.
Points	Points are awarded or subtracted depending on the learner's performance and serve to numerically represent the progression. Points can therefore serve as a reward and as an immediate feedback tool.
Story	A narrative context that serves to contextualise and give meanings to the challenges to be achieved.
Teams	Learners who work together to achieve a common goal. Teams will be broadly regarded here to encompass either cooperative or versus playing.
Time pressure	A time limit that is allowed for the learner to achieve a specific challenge. Time pressure can be illustrated by a countdown timer that indicates to the learner the time remaining.
Virtual goods	Game assets that have a certain in-game value. Virtual goods can sometimes be bought or exchanged using real-world currency.

Supplementary file 1 – PRISMA-P Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	141-142
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-55
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	447-454
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	455-459
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	156-201
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	202-206
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	213-259
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	260-278
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	273-278 Supplementary file 2

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	280-284
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	285-291
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	292-304
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	305-323
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	239-259
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	324-334
DATA					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	351-354
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	355-375
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	376-399
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	410-417
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	335-348
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	400-409

Supplementary file 2 – PubMed search strategy

1. serious gam*[TIAB] OR applied gam*[TIAB] OR ((simulation[TIAB] OR training[TIAB] OR teaching[TIAB] OR educational[TIAB] OR education[TIAB] OR learning[TIAB] OR interactive[TIAB]) AND (((online[TIAB] OR electronic[TIAB] OR digital[TIAB] OR "over-thecounter"[
TIAB] OR commercial[TIAB] OR computer[TIAB] OR virtual[TIAB] OR mobile application*[TIAB] OR mobile app[TIAB]) AND (game[TIAB] OR games[TIAB] OR gamification[TIAB] OR gaming[TIAB] OR)) OR (videogame*[TIAB] OR video game*[TIAB]))
2. "Video Games"[MH]
3. #1 OR #2
4. Health Personnel*[TIAB] OR Health professional*[TIAB] OR Health care profession*[TIAB] OR
Healthcare profession*[TIAB] OR Medical student*[TIAB] OR Medical assistant*[TIAB] OR health worker*[TIAB] OR Audiologist*[TIAB] OR Chiropractor*[TIAB] OR Dentist[TIAB] OR Dentists[TIAB] OR Dietitian*[TIAB] OR Dermatolog*[TIAB] OR endocrinologist*[TIAB] OR Gastroenterolog*[TIAB] OR Gynecolog*[TIAB]OR Radiolog*[TIAB] OR Medical Staff[TIAB] OR Midwife*[TIAB] OR neurologi*[TIAB] OR nutritionist*[TIAB] OR Nurse[TIAB] OR Nurses[TIAB] OR nursing[TIAB] OR Optometrist*[TIAB] OR Occupational Therapist*[TIAB] OR Patholog*[TIAB] OR Paramedic[TIAB] OR Paediatric[TIAB] OR pediatrician*[TIAB] OR Paediatrician*[TIAB] OR pediatrist*[TIAB] OR pediatric[TIAB] OR Pharmacist*[TIAB] OR Pharmaconomist*[TIAB] OR Pharmacologist*[TIAB] OR Pharmacy technician*[TIAB] OR Phlebotomist*[TIAB] OR Physician OR Podiatrist*[TIAB] OR Psychologist*[TIAB] OR Psychotherapist*[TIAB] OR psychiatrist*[TIAB] OR Physical therapist*[TIAB] OR physiotherapist*[TIAB] OR Respiratory therapist*[TIAB] OR Surgeon*[TIAB] OR surgical [TIAB] OR Clinician*[TIAB] OR Cardiologist*[TIAB] OR medical technician*[TIAB] OR emergency doctor*[TIAB] OR emergentologist*[TIAB] OR clinical officer*[TIAB] OR Community health worker*[TIAB] OR Radiographer*[TIAB] OR Radiotherapist*[TIAB] OR technologist[TIAB] OR Anesthetist*[TIAB] OR Resident[TIAB] OR residents[TIAB] OR trainee[TIAB] OR trainees[TIAB] OR intern[TIAB] OR interns[TIAB]
5. "Health Personnel"[MH] OR "Students, Premedical"[MH] OR "Students, Medical"[MH] OR
"Students, Nursing"[Mesh]
6. "Education, Premedical"[MH] OR "Education, Medical"[MH] OR "Education, Nursing"[MH] OR
"Education, Pharmacy"[MH] OR "Education, Public Health Professional"[MH] OR "Clinical Clerkship"[MH]
7. #4 OR #5 OR 6
8. knowledge*[TIAB] OR aptitude*[TIAB] OR accuracy[TIAB] OR ability[TIAB] OR abilities[TIAB] OR capacity [TIAB] OR capacities[TIAB] OR confidence[TIAB] OR competency[TIAB] OR competencies[TIAB] OR impact*[TIAB] OR skill*[TIAB] OR performance*[TIAB] OR learning outcome*[TIAB] OR training outcome*[TIAB] OR

effectiveness[TIAB] OR efficacy[TIAB] OR improvement*[TIAB] OR innovative*[TIAB] OR innovation*[TIAB] OR retention[TIAB] OR randomised controlled trial[TIAB] OR randomized
controlled trial[TIAB]
9. "Clinical Competence"[MH] "Quality Improvement"[MH] OR "Learning Curve"[MH] OR Knowledge [MH] OR "Educational Measurement"[MH] OR "randomized controlled trial"[PT]
10. #8 OR 9
11. #3 AND #7 AND #10
12. (english[LA] OR french[LA]) AND 2000:2017[DP]
13. #11 AND #12

BMJ Open

Effectiveness of serious games and impact of design elements on engagement and educational outcomes in healthcare professionals and students: a systematic review and meta-analysis protocol.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019871.R2
Article Type:	Protocol
Date Submitted by the Author:	17-Jan-2018
Complete List of Authors:	Maheu-Cadotte, Marc-André; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Cossette, Sylvie ; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Dubé, Veronique; Université de Montréal, Faculty of Nursing; Centre de recherche du CHUM Fontaine, Guillaume; Institut De Cardiologie de Montreal, Research Center; Université de Montréal, Faculty of Nursing Mailhot, Tanya; Université de Montréal, Faculty of Nursing; Institut De Cardiologie de Montreal, Research Center Lavoie, Patrick; Boston College - William F Connell School of Nursing Cournoyer, Alexis; Universite de Montreal Faculte de medecine; Hopital du Sacre-Coeur de Montreal Balli, Fabio; Condordia University Mathieu-Dupuis, Gabrielle; Université de Montréal, School of Librarianship and Information Science
Primary Subject Heading:	Medical education and training
Secondary Subject Heading:	Health informatics
Keywords:	Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, MEDICAL EDUCATION & TRAINING, Information technology < BIOTECHNOLOGY & BIOINFORMATICS

Effectiveness of serious games and impact of design elements on engagement and educational outcomes in healthcare professionals and students: a systematic review and meta-analysis protocol.

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Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Abstract

Introduction: Serious games (SGs) are interactive and entertaining digital software with an educational purpose. They engage the learner by proposing challenges and through various design elements (DEs; e.g. points, difficulty adaptation, story). Recent reviews suggest the effectiveness of SGs in healthcare professionals' and students' education is mixed. This could be explained by the variability in their DEs, which has been shown to be highly variable across studies. The aim of this systematic review is to identify, appraise, and synthesize the best available evidence regarding the effectiveness of SGs and the impact of DEs on engagement and educational outcomes of healthcare professionals and students.

Methods and analysis: A systematic search of the literature will be conducted using a combination of MeSH terms and keywords in CINAHL, EMBASE, ERIC, PsycInFO, PubMed, and Web of Science. Studies assessing SGs on engagement and educational outcomes will be included. Two independent reviewers will conduct the screening as well as the data extraction process. The risk of bias of included studies will also be assessed by two reviewers using the Effective Practice and Organisation of Care (EPOC) criteria. Data regarding DEs in SGs will first be synthesized qualitatively. A meta-analysis will then be performed, if the data allows it. Finally, the quality of the evidence regarding the effectiveness of SGs on each outcome will be assessed using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach.

Ethics and dissemination: As this systematic review only uses already collected data, no Institutional Review Board approval is required. Its results will be submitted in a peer-reviewed journal by the end of 2018.

Systematic review registration: PROSPERO International Prospective Register of Systematic Reviews # CRD42017077424

Strengths and limitations of the review

- A comprehensive and prospectively registered (PROSPERO #CRD42017077424) systematic literature review protocol reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.
- An assessment of the overall quality of the evidence regarding effectiveness of SGs on each outcome, using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach
- The definition of "serious game" in this systematic review is limited by the fact that no consensus prevails in the literature.

Introduction

Education of healthcare professionals and students is of the utmost importance to promote the adoption of best practices and to improve patient safety. In 2013, the World Health Organization underlined a need to train healthcare professionals to face population health needs and health service delivery adapted to epidemiological and demographic realities.[1] Engagement, defined as a learner's involvement and interest towards an educational intervention, has been positively correlated with educational outcomes such as learning and behavior change.[2 3] Designing educational interventions to sustain the engagement of healthcare professionals and students is therefore critical to their effectiveness. As such, the last decade has seen a growing interest from researchers about the use of serious games (SGs) in healthcare professionals' and students' education.[4]

Serious games are designed as entertaining and active learning environments which can be made available on any digital platform (e.g. smartphone, computer). Learning in SGs typically occurs through a gameplay that engages the learner in challenges adapted to his in-game skills. Challenges are defined as subjective experiences that solicit the learners' skills.[5] For example, challenges can require the learner to explore, experiment, compete, or cooperate with other learners.[6 7] Gameplay is defined as a combination of challenges and design elements (DEs).[8]

Design elements (DEs), which can be seen as building blocks or shared features of games (e.g. points, difficulty adaptation, story), are suggested to be instrumental in improving the learner's engagement in SGs.[4 9 10] Therefore, a SG may be composed of several DEs and these DEs may be similar across SGs. [11] A list of DEs, based on a literature review by the authors, is presented in Table 1. [10 12-15] Based on Csikszentmihalyi's flow theory and theoretical propositions of other authors in game design, Pavlas suggests that DEs operate by influencing antecedents of engagement such as: the learner's ability to concentrate on task, his sense of control, the feedback he receives, and a deep but effortless involvement.[16] As Lameras et al. underlines the difficulty in linking DEs and engagement to specific learning processes in SGs, it is believed that higher engagement will lead the learner to become deeply involved and to repeatedly take on the challenges offered to improve his in-game performance, and, consequently, his educational outcomes.[17] However, while supporting engagement, there are also concerns that DEs can

become a source of distraction from the learning content and negatively affect educational outcomes.[16 18 19]

Previous reviews have highlighted the mixed effectiveness of SGs when compared to other educational interventions (e.g. classroom learning) in improving healthcare professionals' and students' engagement or educational outcomes.[4 20 21] As previous authors pointed out, the integration of an educational purpose to the gameplay is a delicate process that should be considered throughout SGs development, right up to the initial designing phase of the SGs.[22 23] As such, the mixed effectiveness of SGs in supporting engagement and improving educational outcomes could be explained by the highly variable DEs found in SGs.[24] Moreover, the optimal integration of DEs in SGs remains to be discovered.[22 25] Findings from a recent meta-analysis investigating the effectiveness of SGs on healthy lifestyle promotion underlined the necessity of strong theoretical foundations in designing SGs and the need to further explore which DEs are the most impactful.[26] As the development of SGs can be quite expensive and time-consuming, describing which DEs have been integrated in the development of SGs for healthcare professionals and students, as well as their impact on engagement and educational outcomes, could help in the efficient development of future SGs.[20 27] However, a systematic review of the impact of DEs of SGs on engagement and educational outcomes has yet to be published.

Therefore, our objectives are two-fold: 1) To systematically identify, appraise, and synthesize the best available evidence regarding the effectiveness of SGs on engagement and educational outcomes of healthcare professionals and students; and 2) To describe which DEs have been integrated in the development of SGs for healthcare professionals and students, and their impact on engagement and educational outcomes.

Methods

The protocol for this systematic review was developed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P; see supplementary file 1) and follows the guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions.[28 29] The protocol was also registered prospectively on the PROSPERO International Prospective Register of Systematic Reviews (# CRD42017077424).

Eligibility criteria

The eligibility of studies will be assessed based on study characteristics, participants, interventions assessed, comparators, and the outcome measures for inclusion in the systematic review and the meta-analysis.

Study characteristics

Primary studies published in English or in French from January 1st 2005 to December 31th 2017 will be considered. Previous reviews on SGs have identified a growth in published literature starting mid-2000's[24 30]; and no experimental study assessing an SG for healthcare professionals' and students' education was found before that date.[4] As suggested Effective Practice and Organisation of Care (EPOC) Cochrane Review Group, randomised controlled trials and cluster randomised controlled trials will be included in the current review.[31]

Types of participants

Studies with healthcare professionals and healthcare students from undergraduate to postgraduate education, either in a clinical or an academic setting will be considered. Clinical settings include all environments in which healthcare is provided. Studies conducted exclusively among patients or students receiving non-healthcare related education (e.g. high school students) are beyond the scope of this review as the objectives of the games evaluated in these populations (e.g. illness self-management in patients, the learning of mathematical concepts in students) differ from those developed for healthcare professionals and healthcare students.

Types of interventions

Studies assessing a SG as a stand-alone intervention, or as part of multi-component intervention (e.g. combined with workshop, classroom or digital-based learning) will be considered. For this systematic review, we define SGs as interactive and entertaining digital software with a primary educational purpose that engage a learner through various challenges.[5 8 32 33]

Types of comparators

We will consider studies where the comparator is any type of educational intervention.

Types of outcome measures

Studies reporting at least one measure of engagement or educational outcomes will be considered.

We will retain the definition and the indicators of engagement reported by Perski et al., who defined engagement as: 1) the extent of a learner's involvement; and 2) a subjective experience characterised by affect, attention, and interest.[3] These two dimensions will be considered individually. Regarding involvement, we will look individually at the duration and the frequency of SGs usage, either self-reported or electronically measured by the SGs. Regarding subjective experience, we will consider individually all self-reported measures of the learner's experience while using the SG.

We will define the educational outcomes, which are learning and behavior change, according to the levels of evaluation proposed by Kirkpatrick.[34] Learning represents the knowledge that was acquired (i.e. factual knowledge; e.g. knowledge about the physiopathology of a specific disease), the skills that were improved (i.e. how to perform a certain procedure; e.g. ultrasound needle placement), or the attitudes that were changed (i.e. how worthwhile the learner believes it is to apply the learning in his day-to-day role; e.g. attitudes towards pain management) after playing the SG. These three dimensions will be considered separately (i.e. knowledge, skills, and attitude). Behavior change represents a change in the day-to-day role of the healthcare professionals or the students after playing the SG (e.g. coronary heart disease patients' referral to cardiac rehabilitation by healthcare professionals). For this review, we will consider studies reporting both subjective (e.g. self-reported evaluation) and objective measures (e.g. quiz) of learning and behavior change.

Information sources

Bibliographical databases

Eligible primary studies will be identified through a comprehensive search of six bibliographical databases: Cumulative Index of Nursing and Allied Health (EBSCO), EMBASE (OVID), ERIC (ProQuest), PsycINFO (APA PsycNET), PubMed (NCBI), and Web of Science – SCI and SSCI (ISI – Thomson Scientific).

Hand searching

Relevant journals will be hand-searched for additional articles. Such journals include, but are not limited to: Games for Health Journal, *Games, G|A|M|E The Italian Journal of Game Studies, International Journal of Computer Games Technology, International Journal of Serious Games,* and *JMIR Serious Games*. We will also hand-search for additional articles the reference lists of identified studies and previous systematic reviews related to the use of serious games in healthcare care professionals and healthcare students.

Search strategy for bibliographical databases

The search strategy was collaboratively and iteratively developed with the assistance of a librarian. We initially developed the search strategy for PubMed using a combination of medical subject headings (MeSH) and keyword related to the following key concepts: serious games, healthcare professionals/ healthcare students, and effect on educational outcomes. The search strategy was then translated for the other bibliographical databases (see supplementary file 2).

Study records

Data management

All collected references will be imported and managed in EndNote (Version X8, Clarivate Analytics). Based on the eligibility criteria, we will manage and categorize references in specific files and sub-files inside the software. Full-texts will be uploaded in the software at the corresponding stage of the selection process.

Selection process

Three reviewers will independently perform the selection process of the collected references. The titles and the abstracts will be screened by applying the previously stated eligibility criteria. A full-text assessment of the remaining references will then be performed. We will resolve all disagreements through discussion and consensus. Reasons for excluding references will be documented and reported in a PRISMA flow diagram at the full-text assessment stage of the selection process.[35]

Data extraction process

Two independent reviewers will independently perform the data extraction process using an adapted electronic format of the Effective Practice and Organisation of Care (EPOC) data extraction template. The original template was developed by the EPOC editorial team to serve as a guide in extracting data from primary studies.[36] The reviewers will pilot the form by individually extracting data from a study and by comparing completed forms. Precisions will be added, and wording will be revised, if needed. Notwithstanding data regarding the studies eligibility, we will extract data regarding the impact of the DEs of the SGs on the previously stated outcomes. Data related to the DEs will be extracted during actual gameplay if the SG is publicly available. When it is not possible, data related to the DEs will be extracted based on the information provided in the article. A Kappa statistic will serve to illustrate agreement between the two independent reviewers on the extraction of DEs due to the challenge that could represent this step. Data needed to assess the risk of bias (e.g. allocation concealment, blinding) will also be extracted. All data items to be collected are listed below. When data adjusted for baseline differences between groups are available, we will use them to compute effect sizes. When adjusted data are not available in the article, we will use the unadjusted data. All corresponding authors will be contacted in the case of unclear or missing data in the published articles. We will enter all data in RevMan (Version 5.3, The Cochrane Collaboration), a software which allows data management and analysis during the process of a systematic review and a meta-analysis.[37]

Data items

To guide the extraction of data items related to DEs, a list of DEs was identified through a literature search by the authors (see Table 1).[10 12-14] Accordingly, we will extract the following data items from the included studies:

- To a descriptive purpose: study setting; participants' inclusion and exclusion criteria; study aim; design employed; unit of allocation (e.g. individual, group); start and end dates of the study; duration of participation; unit of measurement; time points measured; tool used to measure the outcome; validity of the tools; name of the SG evaluated; theoretical framework used for the SG development; cost and duration of the SG development; clinical topic addressed in the SG; method of delivery of the comparator intervention (e.g. e-learning, face-to-face), duration and frequency of use of the comparator intervention, clinical topic addressed in the comparator intervention;
- To a meta-analytic purpose: study population; sample size; statistical differences at baseline between groups; DEs in the SG evaluated (see Table 1); duration of SG usage; frequency of SG usage; outcomes related to the learner's subjective experience while using the SG (e.g. interest, flow), knowledge acquisition, skill improvement, and attitude and behavior change; risk of bias data (as outlined below).

Assessment of risk of bias

Two authors will independently assess the risk of bias of included studies using the EPOC criteria.[38] Nine criteria are used and, for each one of them, the study can be judged at "low risk", "high risk", or "unclear risk" of bias. A high risk of bias diminishes the reliability of the study's results. The criteria account for aspects regarding the allocation sequence and concealment, measurements and characteristics of baseline outcome, incomplete outcome data, selective outcome reporting, contamination, blinding, and other risk of bias. Specific guidance to evaluate the risk of bias individually for each criterion is provided by EPOC. Each criterion will be considered independently and no attempt at assigning an overall score at each study will be made, as suggested by EPOC.[38] We will resolve all disagreements about the risk of bias assessment of the two authors through discussion and, if needed, with the help of a third review author.

Assessment of selective reporting of outcomes

We will assess the selective reporting of outcomes by comparing the outcomes reported in the primary study with the ones stated in the published research protocol. If no published research protocol is available, we will check if the study was prospectively registered and compare the outcomes reported in the primary study with the ones in the registration form. If the study was not prospectively registered, we will compare the outcomes presented in the methods section with the ones reported in the results section. In all cases, the corresponding authors of studies for which there are discrepancies in the outcomes reported will be contacted by e-mail to obtain relevant unreported data.

Assessment of publication bias

If more than 10 studies are included in the meta-analysis, we will assess publication bias by constructing a funnel plot with RevMan (Version 5.3, The Cochrane Collaboration).[37] The interpretation of the funnel plot will follow the guidance included in Cochrane Handbook for Systematic Reviews of Interventions .[28] If not, the assessment of publication bias will be done qualitatively.

Data synthesis

Quantitative data synthesis

The meta-analysis will evaluate the effectiveness of SGs on healthcare professionals' and students' engagement (i.e. duration and frequency of SGs usage; outcomes related to the learner's subjective experience while using the SG) and educational outcomes (i.e. knowledge acquisition, skill improvement, and attitude and behavior change). The meta-analysis will only include low risk of bias studies based on the assessment using the EPOC criteria.[38] In the case of serious reporting or publication bias, no meta-analysis will be performed. This decision will be made by consensus between review authors while also considering clinical and methodological diversity.[28]

When multiple trial arms are reported in a single trial, we will include only the relevant arms according to the intervention received and the comparison made (i.e. SG versus any type of educational intervention). If multiple independent comparisons are relevant in a single study (i.e. no common group between comparisons), we'll include individually all comparisons in the meta-

analysis. If one or more groups are shared between comparisons, we'll first try to combine several groups in order to create a single pair-wise comparison. If it's not possible, we'll split the participants in the "shared group" into multiple subgroups, with smaller sample size, to allow pair-wise comparisons. No minimal number of participants per arm will be required in order for a study to be initially included in the meta-analysis.

Random-effects models will be used to pool weighted effect sizes. It is assumed, by using random-effects models, that intervention effect across studies follow a distribution and are not all giving an estimate of the same intervention effect.[28] The decision to use random-effect models was made due to the expected variability between SGs (notably on DEs) and in study design. Pooled weighted effect sizes will be calculated with 95% confidence interval for each outcome. Continuous outcomes that were obtained by using different measures will be grouped by using standardised mean differences. The significance of the effect sizes will be determined using Cohen's classification (<0.2=negligible; 0.2–0.49=small; 0.5–0.8=moderate; >0.8=large).[39] We will define a statistically significant result by a two-sided alpha of 0.05. All quantitative data synthesis will be realized using RevMan (Version 5.3, The Cochrane Collaboration).[37]

Assessment of heterogeneity

Statistical heterogeneity represents the inconsistency of the studies' results and the percentage of variation across studies that is not due to chance.[40] We will assess statistical heterogeneity using the Chi² test and the I^2 statistic within RevMan (Version 5.3, The Cochrane Collaboration).[37] A I^2 value superior to 50% will be considered as a high level of heterogeneity.

Subgroup analysis

We will try to explain the source of statistical heterogeneity by exploring clinical and methodological diversity through subgroup analyses. Following the guidance of the Cochrane Handbook for Systematic Reviews of Interventions, caution is required in comparing the magnitude of effect between subgroups as these results remain observational. Therefore, these subgroup analyses will serve primarily to investigate heterogeneity and will be conducted when at least two studies can be included in an individual subgroup.

1. **Population:** Whether current healthcare professionals or students are the focus of the study.
2. **Intervention:** Whether the serious game was delivered as a stand-alone intervention or as part of a multi-component intervention.

3. **Publication year:** Whether the study was published before or after 2014. As SG development is intrinsically linked to the technological state at a given moment, it is suggested that the overall quality of SGs should have improved in the last couple of years, and similarly their effectiveness in supporting engagement and improving educational outcomes.[30] In parallel, the New Media Consortium declared in 2014 that the use of SGs was to be significantly experimented by educational institutions in the next two to three years.[41]

Sensitivity analyses

Sensitivity analyses will be performed to evaluate if the exclusion of small studies would affect the findings of the meta-analysis and the statistical heterogeneity for each previously stated outcome. If, after exclusion of small studies (if appropriate), at least three studies included in the meta-analysis evaluated SGs containing a specific DE (see Table 1), we will perform sensitivity analyses to evaluate the impact of this DE on engagement and educational outcomes. This minimal number of studies (3) is necessary to minimize, during analysis, the potential risk of homogeneity in the DEs integrated to the SGs.

Assessment of the overall quality of evidence

The quality of the evidence regarding the overall effectiveness of SGs and each outcome will be assessed by using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach.[42] GRADE formalizes the process of evaluating the overall quality of evidence and formulating recommendations. For each individual outcome, there are four levels of quality of evidence (very low, low, moderate, high) which represent our confidence in the estimate of effect. Quality of evidence depends on factors such as risk of bias, unexplained heterogeneity, and indirectness of the evidence. Two authors will independently assess and justify the quality of evidence regarding the overall effectiveness of SGs on each selected outcome. All disagreements will be resolved through discussion and consensus.

Qualitative data synthesis

A qualitative data synthesis will be presented whether or not a meta-analysis will have been performed. Descriptive data (e.g. year published, country of origin, population, sample size, study design, name of the SG assessed, clinical topic addressed, outcomes measured) of each included study will be presented in a tabular form. A summary table containing an overview of

all DEs included in the SGs assessed will also be presented. The results according the overall effectiveness of SGs, and the impact of DEs on engagement and educational outcomes will be presented narratively.

Ethics and dissemination

As this systematic review only use already collected data, no ethics approval is required. The review is currently registered (PROSPERO #CRD42017077424). We plan to submit the results in a peer-reviewed journal by the end of 2018.

Discussion

This systematic review will fulfill important needs in the designing of SGs for healthcare professionals' and students' education. As previous systematic reviews focused on a narrative evaluation of the overall effectiveness of SGs in the healthcare professions[4 21 43 44], to our knowledge, this will be the first systematic review to describe and evaluate of the impact of the pre-specified DEs on engagement and educational outcomes. Previous systematic reviews were able to quantify the impact of several DEs in simulation (e.g. range of task difficulty, deliberate practice)[45 46] and internet-based education (e.g. integration of an online discussion forum and audio files).[47] Depending on the quantity of data available, planned sensitivity analyses will allow the quantitative evaluation of the impact of the DEs on selected outcomes. However, we acknowledge that possible homogeneity in DEs integrated to SGs could represent a limit to planned sensitivity analysis.

The protocol of this systematic review is prospectively registered (PROSPERO #CRD42017077424) and is reported according to the PRISMA-P guidelines.[29] Our research strategy was collaboratively designed with the assistance of a librarian and will extensively cover several relevant databases. However, as clear criteria have yet to be established in the literature regarding what can be considered a SG, we will adopt an inclusive definition that does not discriminate based on the SG genre (e.g. quiz, adventure).[5 8 32 33] In the case of ambiguity regarding the inclusion of specific studies due to the nature of the of intervention, review authors will assess their eligibility through discussion and consensus. Nonetheless, this limitation will be addressed in the reporting of the full systematic review and considered in the formulation of recommendations. Moreover, as the integration of the selected DEs in SGs developed for

healthcare professionals and students is currently unknown, it is currently planned to describe the integration of these DEs in developed SGs and their alignment with theoretical foundations, as stated by the authors.

Authors' contributions

All authors contributed to the conception of the protocol. MAMC wrote the initial draft of the protocol. SC, VD, GF, TM, PL, AC, FB, and GMD critically revised the initial draft for important intellectual content. All authors gave final approval of the manuscript submitted. All authors agreed to be accountable for all aspects related to this work.

Acknowledgements

This research was carried out as part of the doctoral studies of the first author and for which he received scholarships from the followings: Montreal Heart Institute Foundation, Ministère de l'Éducation et de l'Enseignement supérieur du Québec, Faculty of Nursing of the Université de Montréal, Fondation J.A. DeSève, and Fondation Alice-Girard.

Data sharing

No additional data available.

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Table 1. Design elements in serious games to be assessed

Design elements	
Avatars	The learner chooses or creates a graphical representation of himself in the serious game.
Badges for achievement	A visual representation that serves as a symbol for the learner's achievements.
Content unlocking	Access to new aspects of the serious game (e.g. higher levels) when certain tasks have been accomplished.
Difficulty adaptation	Levels of difficulty of the challenges can be adjusted by the learner (e.g. easy, medium, and hard) or automatically adjusted to the learner's performance.
Hints	A suggestion or an indication given by the serious game to help the learner achieve a challenge. A learner may choose to receive a hint or the serious game can give hints based on his performance.
Leaderboard	A table or a graph that ranks the learners according to their success based on specific criteria.
Performance tables or graphs	A table or a graph that provides information to the learner about the progression of his performance over time.
Plot	A narrative discourse that serves to organize the events of a story in a logical or temporal order.
Points	Points are awarded or subtracted depending on the learner's performance and serve to numerically represent the progression. Points can therefore serve as a reward and as an immediate feedback tool.
Teams	Learners who work together to achieve a common goal. Teams will be broadly regarded here to encompass either cooperative or versus playing.
Time pressure	A time limit that is allowed for the learner to achieve a specific challenge. A time limit can be illustrated by a countdown timer that indicates to the learner the time remaining.
Virtual goods	Game assets that have a certain in-game value. Virtual goods can sometimes be bought or exchanged using real-world currency.

Supplementary file 1 – PRISMA-P Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	141-142
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-55
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	462-467
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	467-471
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	156-201
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	202-206
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	213-261
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	262-280
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	275-280 Supplementary file 2
STUDY RECORDS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	282-286
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	287-293
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	294-312
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	313-329
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	240-261
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	330-340
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	361-364

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	365-388
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	389-414
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	425-432
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	341-355
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	415-424

Supplementary file 2 – PubMed search strategy

1. serious gam*[TIAB] OR applied gam*[TIAB] OR ((simulation[TIAB] OR training[TIAB] OR teaching[TIAB] OR educational[TIAB] OR education[TIAB] OR learning[TIAB] OR interactive[TIAB]) AND (((online[TIAB] OR electronic[TIAB] OR digital[TIAB] OR "over-thecounter"[
TIAB] OR commercial[TIAB] OR computer[TIAB] OR virtual[TIAB] OR mobile application*[TIAB] OR mobile app[TIAB]) AND (game[TIAB] OR games[TIAB] OR gamification[TIAB] OR gaming[TIAB] OR)) OR (videogame*[TIAB] OR video game*[TIAB])))
2. "Video Games"[MH]
3. #1 OR #2
4. Health Personnel*[TIAB] OR Health professional*[TIAB] OR Health care profession*[TIAB] OR
Healthcare profession*[TIAB] OR Medical student*[TIAB] OR Medical assistant*[TIAB] OR health worker*[TIAB] OR Audiologist*[TIAB] OR Chiropractor*[TIAB] OR Dentist[TIAB] OR Dentists[TIAB] OR Dietitian*[TIAB] OR Dermatolog*[TIAB] OR endocrinologist*[TIAB] OR Gastroenterolog*[TIAB] OR Gynecolog*[TIAB]OR Radiolog*[TIAB] OR Medical Staff[TIAB] OR Midwife*[TIAB] OR neurologi*[TIAB] OR nutritionist*[TIAB] OR Nurse[TIAB] OR Nurses[TIAB] OR nursing[TIAB] OR Optometrist*[TIAB] OR Occupational Therapist*[TIAB] OR Patholog*[TIAB] OR Paramedic[TIAB] OR Paediatric[TIAB] OR pediatrician*[TIAB] OR Paediatrician*[TIAB] OR pediatrist*[TIAB] OR pediatric[TIAB] OR Pharmacist*[TIAB] OR Pharmaconomist*[TIAB] OR Pharmacologist*[TIAB] OR Pharmacy technician*[TIAB] OR Phlebotomist*[TIAB] OR Physician OR Podiatrist*[TIAB] OR Psychologist*[TIAB] OR Psychotherapist*[TIAB] OR psychiatrist*[TIAB] OR Physical therapist*[TIAB] OR physiotherapist*[TIAB] OR Respiratory therapist*[TIAB] OR Surgeon*[TIAB] OR surgical [TIAB] OR Clinician*[TIAB] OR Cardiologist*[TIAB] OR medical technician*[TIAB] OR emergency doctor*[TIAB] OR emergentologist*[TIAB] OR clinical officer*[TIAB] OR Community health worker*[TIAB] OR Radiographer*[TIAB] OR Radiotherapist*[TIAB] OR technologist[TIAB] OR Anesthetist*[TIAB] OR Resident[TIAB] OR residents[TIAB] OR trainee[TIAB] OR trainees[TIAB] OR intern[TIAB] OR interns[TIAB]
5. "Health Personnel"[MH] OR "Students, Premedical"[MH] OR "Students, Medical"[MH] OR
"Students, Nursing"[Mesh]
6. "Education, Premedical"[MH] OR "Education, Medical"[MH] OR "Education, Nursing"[MH] OR
"Education, Pharmacy"[MH] OR "Education, Public Health Professional"[MH] OR "Clinical Clerkship"[MH]
7. #4 OR #5 OR 6
8. knowledge*[TIAB] OR aptitude*[TIAB] OR accuracy[TIAB] OR ability[TIAB] OR abilities[TIAB] OR capacity [TIAB] OR capacities[TIAB] OR confidence[TIAB] OR competency[TIAB] OR competencies[TIAB] OR impact*[TIAB] OR skill*[TIAB] OR performance*[TIAB] OR learning outcome*[TIAB] OR training outcome*[TIAB] OR

effectiveness[TIAB] OR efficacy[TIAB] OR improvement*[TIAB] OR innovative*[TIAB] OR innovation*[TIAB] OR retention[TIAB] OR randomised controlled trial[TIAB] OR randomized
controlled trial[TIAB]
9. "Clinical Competence"[MH] "Quality Improvement"[MH] OR "Learning Curve"[MH] OR Knowledge [MH] OR "Educational Measurement"[MH] OR "randomized controlled trial"[PT]
10. #8 OR 9
11. #3 AND #7 AND #10
12. (english[LA] OR french[LA]) AND 2000:2017[DP]
13. #11 AND #12