Exploring the relationship between all-cause and cardiac-related mortality following COVID-19 vaccination in Florida residents: a self-controlled case series study

Objectives: To evaluate the risks of all-cause and cardiac-related mortality following COVID-19 vaccination by age, sex, and vaccination type. Additionally, previous studies have shown risk of myocarditis/pericarditis is highest among males aged 16-39 who have received an mRNA vaccination, thus, a cardiac-related high-risk group was evaluated.[1]

Design: Self-controlled case series (SCCS) adapted to evaluate death as the outcome.[2] The SCCS method, originally developed to assess vaccine safety, utilizes within-person comparisons to estimate the temporal association between a transient exposure and an acute event.[2] The SCCS method estimates relative incidence (RI) by comparing incidence during a defined high-risk period following exposure with incidence during a control period (i.e., all time in the follow-up period that is not the risk period).[2–5] A major strength of the SCCS method is that fixed-time confounders, such as health related risk-factors, are controlled for.[2,3]

Data sources: Data from Florida's reportable disease repository (Merlin), Florida State Health Online Tracking System (FLSHOTS), and death records data from vital statistics were linked.

Setting and study population: Florida residents aged 12 years and older who died within 18-weeks of COVID-19 vaccination were included. Individuals were excluded if they (1) had a documented COVID-19 infection during the 18-week follow-up period, (2) experienced a COVID-19 associated death, or (3) received their last COVID-19 vaccination after February 25, 2022 (to ensure each individual had the 18-week follow-up period to experience the event of interest). The final study population consisted of 42,076 individuals.

Exposure and outcomes: The exposure of interest was the six-week period following each individual's last COVID-19 vaccination. The six-week risk period was also divided into individual weeks to assess if there was an indication of increased risk during any of the weeks comprising the whole risk-period.

Three outcomes were assessed. Natural all-cause deaths (i.e., excluding homicides, suicides, and accidents), natural all-cause and unknown deaths, and cardiac-related deaths. Cardiac-related deaths were included if their death record contained an ICD-10 code of I30-I52. Only participants that experienced the exposure and outcome were included in this study.

Statistical analysis: Follow-up began on the day of last COVID-19 vaccination. Participants were not censored upon death, rather, they were followed for the entire 18-week follow-up period.[2–5]

Conditional logistic regression models offsetting by interval-length were used to estimate RIs and 95% confidence intervals (CIs) comparing incidence in the risk period (i.e., weeks 1-6) to incidence in the baseline period (i.e., weeks 7-18).[5,6] Seasonality was controlled for in each model unless the sample size was too small. Potential confounding by age was reduced by limiting the follow-up period to 18-weeks. Separate models were fitted for each outcome and subgroup analyzed. Estimates were considered statistically significant if the 95% CI did not contain 1.

Data wrangling, cleaning, and preprocessing were performed with R version 4.1.0. Data were formatted into a stacked dataset, where exposures for each individual are stacked in columns (i.e., multiple rows

per individual), using the SCCS package. Conditional logistic regression models were estimated using the clogit function from the survival package.

Results: Table 1 presents the results for each of the three outcomes assessed for the entire study population and by age groups. Risk for each outcome assessed was significantly lower during the risk period for the whole study population and most age-groups. There was no evidence of increased risk following vaccination for any of the outcomes assessed.

Table 2 presents the results for broader age groups (to increase sample size for stratification) stratified by sex and vaccination type for each outcome. Figures 1 and 2 display these results for natural all-cause and cardiac-related deaths, respectively. Most estimates indicate a significant decrease in risk during the risk period. There were no indications of increased risk following vaccination.

Table 3 presents the results for the cardiac-related high-risk group (i.e., males who received an mRNA vaccination). Figure 3 displays the results for the 25-39 age group for natural all-cause and cardiac-related deaths. No significant increase in risk following vaccination was observed for each of the outcomes assessed.

Conclusion: In this statewide study involving vaccinated persons aged 12 years or older in Florida, no increase in the incidence of natural all-cause, natural all-cause/unknown, or cardiac-related deaths was detected following COVID-19 vaccination. Significant decreases in death incidence following vaccination were observed for some groups evaluated. This decrease in risk following vaccination is likely due to healthy vaccinee bias,[7] where individuals are healthier at the time of vaccination, and with time, their health may decline.

Table 1: Relative incidence of natural all-cause, natural all-cause and unknown, and cardiac-related deaths by age group during each week in the risk period and the six-week risk period vs the baseline period*

	All-cause deaths		
	Natural	**Natural and unknown**	**Cardiovascular related deaths**
Subgroup, risk period	**RI (95% CI)**	**RI (95% CI)**	**RI (95% CI)**
All ages			
Week 1	0.36 (0.34 - 0.39)	0.37 (0.34 - 0.39)	0.40 (0.36 - 0.45)
Week 2	0.62 (0.59 - 0.66)	0.63 (0.59 - 0.66)	0.67 (0.61 - 0.73)
Week 3	0.78 (0.74 - 0.82)	0.79 (0.75 - 0.83)	0.83 (0.77 - 0.91)
Week 4	0.84 (0.80 - 0.88)	0.84 (0.80 - 0.88)	0.85 (0.78 - 0.92)
Week 5	0.91 (0.87 - 0.96)	0.91 (0.87 - 0.95)	0.93 (0.86 - 1.01)
Week 6	0.95 (0.90 – 0.99)	0.94 (0.90 - 0.98)	0.95 (0.88 - 1.02)
Weeks 1-6	**0.76 (0.74 - 0.78)**	**0.76 (0.74 - 0.78)**	**0.79 (0.76 - 0.83)**
Ages 16-24			
Week 1	NA	NA	NA
Week 2	NA	NA	NA
Week 3	NA	NA	NA
Week 4	NA	NA	NA
Week 5	NA	NA	NA
Week 6	NA	NA	NA
Weeks 1-6	**0.56 (0.24 - 1.30)**	**0.79 (0.37 - 1.79)**	**0.53 (0.18 - 1.61)****
Ages 25-39			
Week 1	0.41 (0.20 - 0.86)	0.43 (0.22 - 0.84)	1.13 (0.49 - 2.61)
Week 2	0.47 (0.24 – 0.93)	0.47 (0.25 – 0.90)	0.82 (0.32 - 2.12)
Week 3	0.62 (0.34 - 1.13)	0.71 (0.41 - 1.20)	0.82 (0.32 - 2.09)
Week 4	0.78 (0.46 - 1.33)	0.80 (0.48 - 1.32)	0.98 (0.41 - 2.34)
Week 5	0.78 (0.46 - 1.33)	0.80 (0.48 - 1.32)	0.84 (0.33 - 2.13)
Week 6	0.73 (0.42 - 1.27)	0.71 (0.42 - 1.20)	1.36 (0.64 - 2.90)
Weeks 1-6	**0.64 (0.48 - 0.85)**	**0.66 (0.50 - 0.86)**	**1.00 (0.63 - 1.59)**
Ages 40-59			
Week 1	0.50 (0.39 - 0.62)	0.49 (0.39 - 0.61)	0.48 (0.31 - 0.73)
Week 2	0.66 (0.54 - 0.81)	0.65 (0.54 - 0.80)	0.86 (0.63 - 1.19)
Week 3	0.79 (0.66 - 0.95)	0.78 (0.65 - 0.94)	0.91 (0.67 - 1.24)
Week 4	0.89 (0.74 - 1.06)	0.87 (0.73 - 1.03)	0.96 (0.71 - 1.29)
Week 5	0.94 (0.80 - 1.12)	0.94 (0.80 - 1.11)	0.89 (0.65 - 1.20)
Week 6	0.91 (0.77 - 1.08)	0.91 (0.77 - 1.07)	0.89 (0.65 - 1.20)
Weeks 1-6	**0.79 (0.72 - 0.87)**	**0.78 (0.71 - 0.86)**	**0.84 (0.71 – 0.99)**
Ages 60-80			
Week 1	0.35 (0.31 - 0.39)	0.35 (0.31 - 0.39)	0.40 (0.33 - 0.48)
Week 2	0.57 (0.52 - 0.62)	0.57 (0.52 - 0.63)	0.62 (0.53 - 0.72)
Week 3	0.73 (0.68 - 0.80)	0.74 (0.69 - 0.81)	0.84 (0.73 - 0.95)
Week 4	0.81 (0.75 - 0.87)	0.81 (0.75 - 0.87)	0.84 (0.74 - 0.96)
Week 5	0.89 (0.83 - 0.96)	0.89 (0.83 - 0.96)	0.94 (0.83 - 1.06)
Week 6	0.92 (0.86 – 0.99)	0.92 (0.85 - 0.98)	0.95 (0.84 - 1.07)
Weeks 1-6	**0.73 (0.70 - 0.76)**	**0.73 (0.70 - 0.76)**	**0.78 (0.73 - 0.84)**

Ages >80			
Week 1	0.36 (0.32 - 0.40)	0.36 (0.33 - 0.40)	0.38 (0.32 - 0.45)
	All-cause deaths		
	Natural	**Natural and unknown**	**Cardiovascular related deaths**
Subgroup, risk period	**RI (95% CI)**	**RI (95% CI)**	**RI (95% CI)**
Week 2	0.66 (0.61 - 0.72)	0.66 (0.61 - 0.72)	0.67 (0.59 - 0.77)
Week 3	0.81 (0.76 - 0.88)	0.82 (0.76 - 0.88)	0.82 (0.72 - 0.92)
Week 4	0.86 (0.80 - 0.92)	0.86 (0.80 - 0.92)	0.84 (0.74 - 0.94)
Week 5	0.92 (0.86 - 0.99)	0.92 (0.85 - 0.98)	0.93 (0.83 - 1.04)
Week 6	0.96 (0.90 - 1.03)	0.96 (0.90 - 1.03)	0.93 (0.84 - 1.04)
Weeks 1-6	**0.79 (0.76 - 0.83)**	**0.79 (0.76 - 0.83)**	**0.79 (0.74 - 0.85)**

NA = Sample size too small to estimate

*Adjusted for seasonality

**Crude due to sparse data

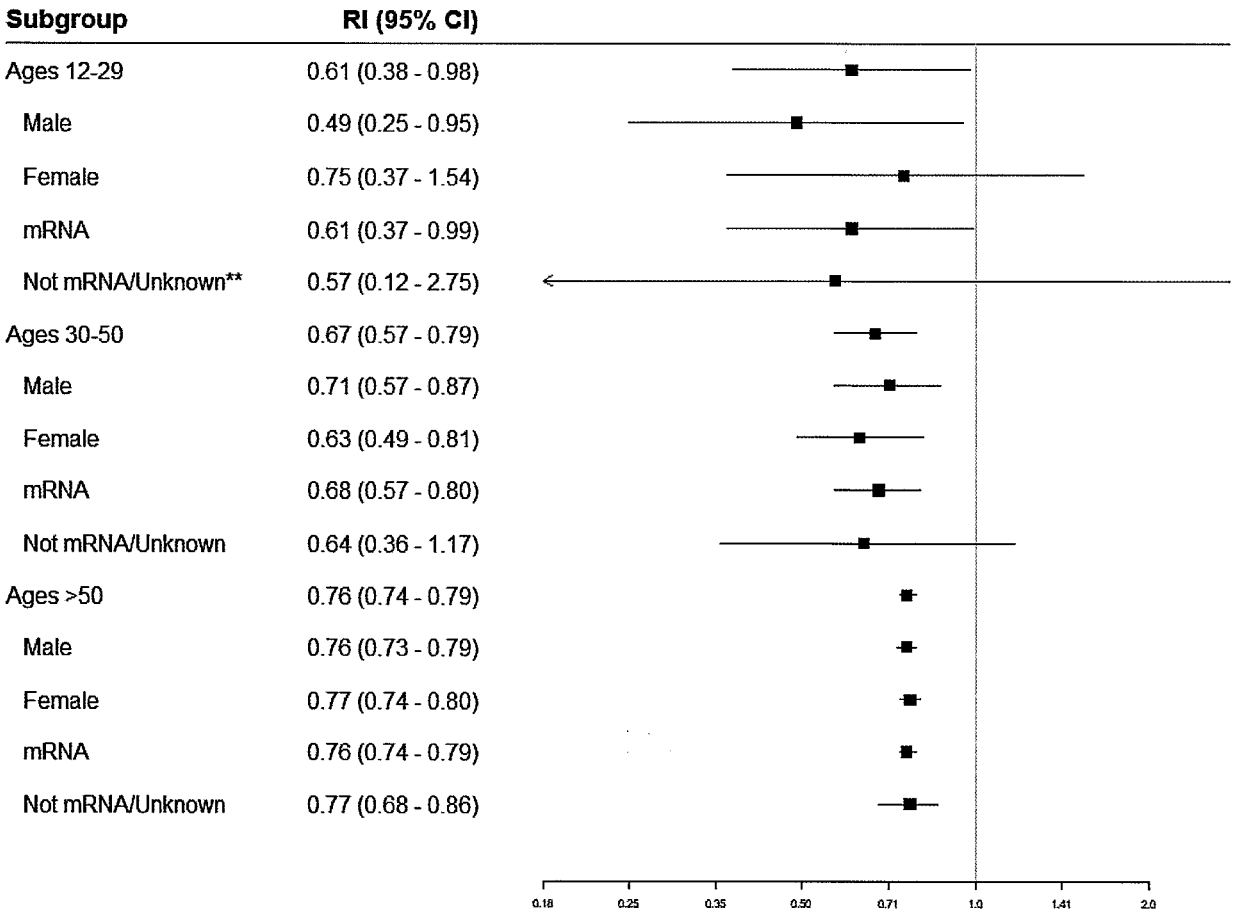
Table 2: Relative incidence of natural all-cause, natural all-cause and unknown, and cardiac-related deaths by age group, sex, and vaccine type during the six-week risk period vs the baseline period*

	All-cause deaths		
	Natural	**Natural and unknown**	**Cardiac-related deaths**
Subgroup, risk period	**RI (95% CI)**	**RI (95% CI)**	**RI (95% CI)**
Ages 12-29	0.61 (0.38 - 0.98)	0.70 (0.45 - 1.08)	0.88 (0.40 - 1.95)
Male	0.49 (0.25 - 0.95)	0.64 (0.36 - 1.13)	0.94 (0.41 - 2.18)**
Female	0.75 (0.37 - 1.54)	0.72 (0.36 - 1.44)	0.75 (0.20 - 2.83)**
mRNA	0.61 (0.37 - 0.99)	0.72 (0.46 - 1.11)	0.87 (0.41 - 1.83)**
Not mRNA/Unknown	0.57 (0.12 - 2.75)**	0.86 (0.22 - 3.32)**	1.00 (0.09 - 11.03)**
Ages 30-50	0.67 (0.57 - 0.79)	0.66 (0.57 - 0.77)	0.74 (0.57 - 0.96)
Male	0.71 (0.57 - 0.87)	0.71 (0.58 - 0.87)	0.75 (0.54 - 1.03)
Female	0.63 (0.49 - 0.81)	0.60 (0.47 - 0.76)	0.71 (0.45 - 1.12)
mRNA	0.68 (0.57 - 0.80)	0.66 (0.57 - 0.78)	0.75 (0.57 - 0.98)
Not mRNA/Unknown	0.64 (0.36 - 1.17)	0.60 (0.35 - 1.05)	0.96 (0.50 - 1.87)**
Ages >50	0.76 (0.74 - 0.79)	0.77 (0.74 - 0.79)	0.79 (0.75 - 0.83)
Male	0.76 (0.73 - 0.79)	0.76 (0.73 - 0.79)	0.80 (0.75 - 0.85)
Female	0.77 (0.74 - 0.80)	0.77 (0.74 - 0.80)	0.78 (0.73 - 0.84)
mRNA	0.76 (0.74 - 0.79)	0.76 (0.74 - 0.79)	0.79 (0.75 - 0.83)
Not mRNA/Unknown	0.77 (0.68 - 0.86)	0.76 (0.68 - 0.85)	0.87 (0.71 - 1.06)

*Adjusted for seasonality

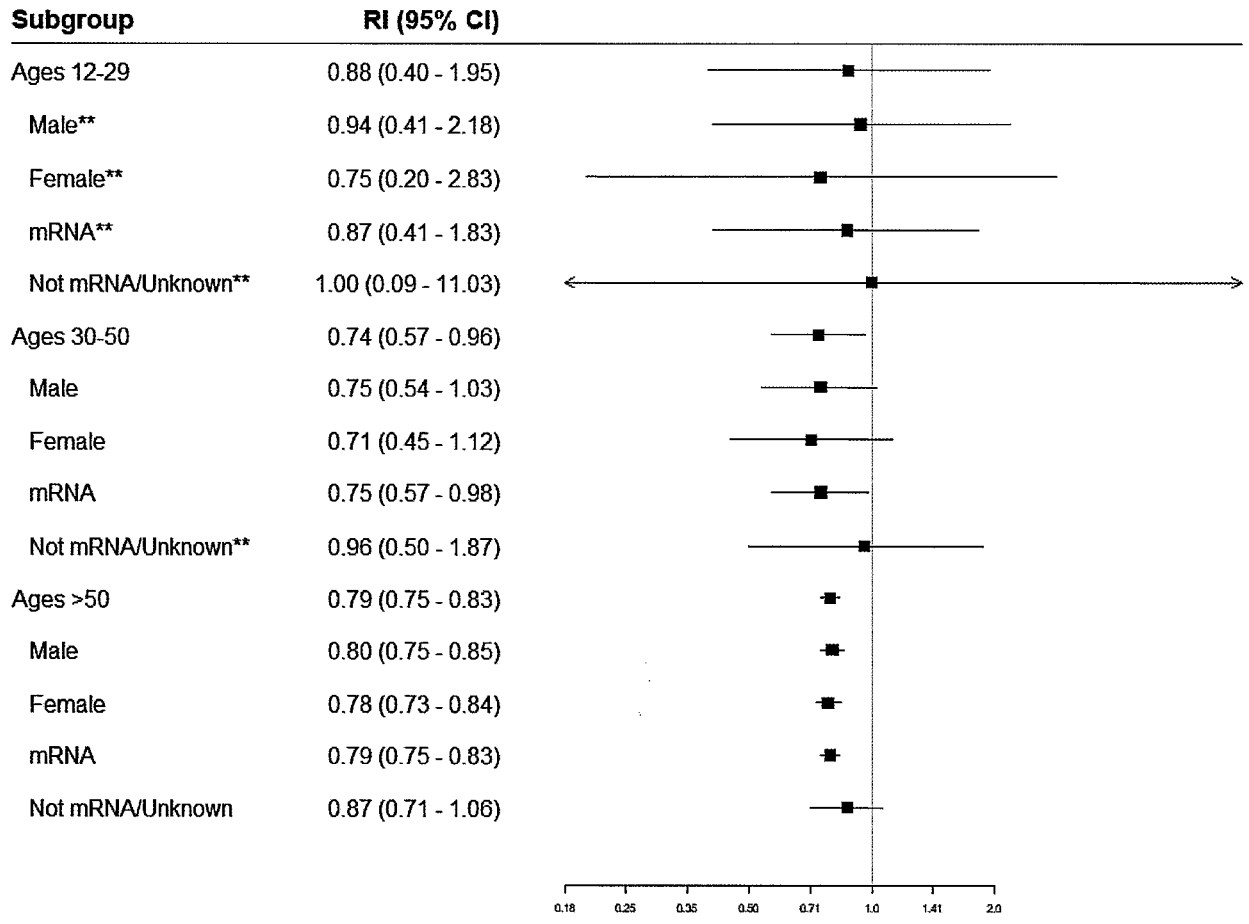
**Crude due to sparse data

Figure 1. Relative incidence of natural all-cause deaths during the six-week risk period vs the baseline period by age group, sex, and vaccine type*



Squares represent relative incidence (RI)
*Adjusted for seasonality
** Crude due to sparse data

Figure 2. Relative incidence of cardiac-related deaths during the six-week risk period vs the baseline period by age group, sex, and vaccine type*



Squares represent relative incidence (RI)
*Adjusted for seasonality
** Crude due to sparse data

Table 3: Relative incidence of natural all-cause, natural all-cause and unknown, and cardiac-related deaths during each week and the six-week risk period vs the baseline period among males who received an mRNA vaccination*

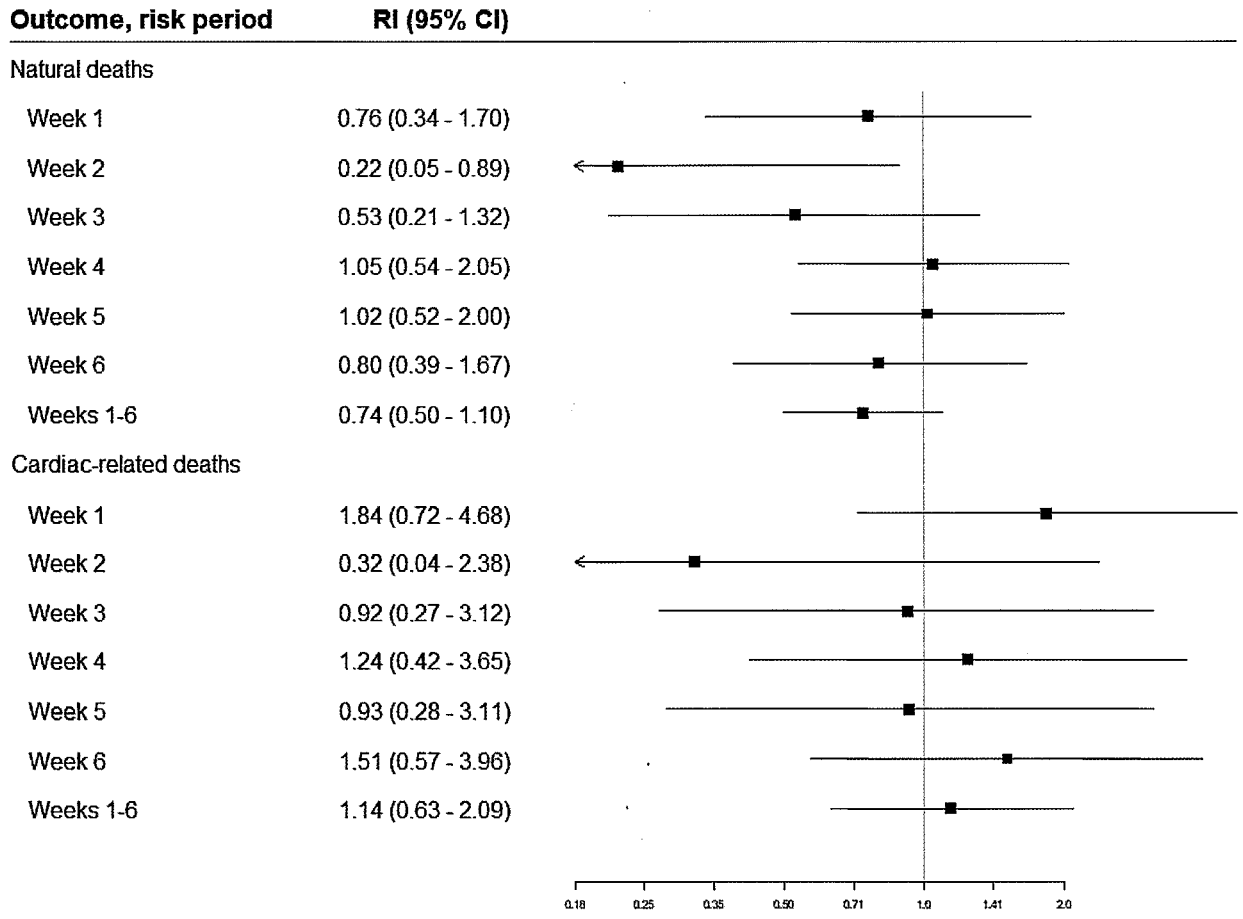
	All-cause deaths		
	Natural	**Natural and unknown**	**Cardiovascular related deaths**
Subgroup, risk period	**RI (95% CI)**	**RI (95% CI)**	**RI (95% CI)**
Ages 16-24			
Week 1	NA	NA	NA
Week 2	NA	NA	NA
Week 3	NA	NA	NA
Week 4	NA	NA	NA
Week 5	NA	NA	NA
Week 6	NA	NA	NA
Weeks 1-6	**0.63 (0.25 – 1.58)****	**0.84 (0.37 – 1.92)****	**0.67 (0.18 – 2.46)****
Ages 25-39			
Week 1	0.76 (0.34 - 1.70)	0.71 (0.33 - 1.57)	1.84 (0.72 - 4.68)
Week 2	0.22 (0.05 - 0.89)	0.30 (0.10 - 0.97)	0.32 (0.04 - 2.38)
Week 3	0.53 (0.21 - 1.32)	0.80 (0.38 - 1.66)	0.92 (0.27 - 3.12)
Week 4	1.05 (0.54 - 2.05)	1.09 (0.58 - 2.06)	1.24 (0.42 - 3.65)
Week 5	1.02 (0.52 - 2.00)	1.17 (0.63 - 2.15)	0.93 (0.28 - 3.11)
Week 6	0.80 (0.39 - 1.67)	0.85 (0.43 - 1.70)	1.51 (0.57 - 3.96)
Weeks 1-6	**0.74 (0.50 - 1.10)**	**0.83 (0.58 - 1.19)**	**1.14 (0.63 - 2.09)**
Ages 40-59			
Week 1	0.50 (0.36 - 0.68)	0.50 (0.37 - 0.69)	0.47 (0.27 - 0.82)
Week 2	0.64 (0.49 - 0.85)	0.63 (0.48 - 0.83)	0.84 (0.55 - 1.28)
Week 3	0.81 (0.63 - 1.05)	0.81 (0.63 - 1.03)	0.96 (0.65 - 1.43)
Week 4	0.92 (0.73 - 1.17)	0.90 (0.71 - 1.14)	0.92 (0.62 - 1.37)
Week 5	0.96 (0.76 - 1.21)	0.98 (0.78 - 1.22)	0.82 (0.54 - 1.25)
Week 6	0.95 (0.75 - 1.19)	0.95 (0.76 - 1.18)	0.82 (0.54 - 1.25)
Weeks 1-6	**0.81 (0.71 - 0.92)**	**0.80 (0.71 - 0.91)**	**0.81 (0.65 - 1.01)**

NA = Sample size too small to estimate

* Adjusted for seasonality

**Crude due to sparse data

Figure 3. Relative incidence of natural all-cause and cardiac-related deaths during each week and the six-week risk period vs the baseline period among males aged 25 to 39 years who received an mRNA vaccination*



Squares represent relative incidence (RI)
*Adjusted for seasonality

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Exploring the relationship between all-cause and cardiac-related mortality following COVID-19 vaccination or infection in Florida residents: a self-controlled case series study

Objectives

To evaluate the risks of all-cause and cardiac-related mortality following COVID-19 vaccination. For context, a similar analysis was conducted for unvaccinated individuals following COVID-19 infection.

Methods

Design

The self-controlled case series (SCCS) method adapted to evaluate death as the outcome was used.[1] The SCCS method, originally developed to assess vaccine safety, utilizes within-person comparisons to estimate the temporal association between a transient exposure and an acute event.[1] The SCCS method estimates relative incidence (RI) by comparing incidence during a defined high-risk period following exposure with incidence during a control period (i.e., all time in the follow-up period that is not the risk period).[1–4] A major strength of the SCCS method is that fixed-time confounders, such as health related risk-factors, are controlled for.[1,2]

Data sources

Data from Florida's reportable disease repository (Merlin), Florida State Health Online Tracking System (FLSHOTS), and death records data from vital statistics were linked.

Setting and study population

For the vaccination analysis, Florida residents aged 18 years or older who died within 25-weeks of COVID-19 vaccination since the start of the vaccination roll-out (December 15, 2020) were included. Individuals were excluded if they (1) had a documented COVID-19 infection, (2) experienced a COVID-19 associated death, (3) received a booster, or (4) received their last COVID-19 vaccination after December 8, 2021 (to ensure each individual had the 25-week follow-up period to experience the event of interest).

For the COVID-19 infection analysis, Florida residents aged 18 years or older who died within 25-weeks of COVID-19 infection since the start of mass testing (July 1, 2020) were included. Individuals were excluded if they were vaccinated or were infected after December 8, 2021. To allow for death registration, the study end date for both analyses was June 1, 2022.

Exposure and outcomes

The exposure of interest was the 28-day risk period following each individual's last COVID-19 vaccination or infection.

Two outcomes were assessed. Natural all-cause deaths (i.e., excluding homicides, suicides, and accidents) and cardiac-related deaths. Cardiac-related deaths were included if their death record contained an ICD-10 code of I30-I52. Only participants that experienced the exposure and outcome were included in this study.

Statistical analysis

For the vaccination analysis, follow-up began on the day of their last COVID-19 vaccination. For the infection analysis, follow-up began on the day of their positive test result. Participants were not censored upon death, rather, they were followed for the entire 25-week follow-up period.[1–4]

Conditional logistic regression models offsetting by interval-length were used to estimate RIs and 95% confidence intervals (CIs) comparing incidence in the 28-day risk period to incidence in the baseline period (i.e., the rest of the follow-up period).[4,5] Seasonality was controlled for in each model unless the sample size was too small. Potential confounding by age was reduced by limiting the follow-up period to 25-weeks. Separate models were fitted for each outcome and subgroup analyzed. Estimates were considered statistically significant if the 95% CI did not contain 1.

Data wrangling, cleaning, and preprocessing were performed with R version 4.1.0. Data were formatted into a stacked dataset, where exposures for each individual are stacked in columns (i.e., multiple rows per individual), using the SCCS package. Conditional logistic regression models were estimated using the clogit function from the survival package.

Results

Table 1 presents the results for natural all-cause and cardiac-related deaths following COVID-19 vaccination or infection for the entire study population and by age groups.

All-cause deaths following vaccination

In the 28 days following vaccination, no increase in risk was observed for all-cause deaths. A significant decrease was observed for participants 60 years or older in the 28 days following vaccination (RI = 0.97, 95% CI = 0.94 - 0.99).

All-cause deaths following infection

A significant increase in risk for all-cause deaths 28 days following COVID-19 infection was observed for the entire study population and for each age group assessed. The adjusted RI for the entire study population following infection was 16.40 (95% CI = 15.99 - 16.83). Risk was highest among participants 60 years of age or older (RI = 18.60, 95% CI = 18.07 - 19.16) and was lowest among participants 25 - 39 years of age (RI = 8.91, 95% CI = 7.59 - 10.47).

Cardiac-related deaths following vaccination

In the 28 days following vaccination, a significant increase in cardiac-related deaths was detected for the entire study population (RI = 1.07, 95% CI = 1.03 - 1.12). Stratifying by age group revealed RIs were significantly higher for age groups 25 - 39 (RI = 2.16, 95% CI = 1.35 - 3.47) and 60 or older (RI = 1.05, 95% CI = 1.01 - 1.10). The remaining age groups failed to reach statistical significance.

Cardiac-related deaths following infection

Incident rates were significantly higher during the 28-day risk period following infection when compared to the baseline for the entire study population and each age group. The adjusted RI for the entire study population was 18.24 (95% CI = 17.27 - 19.26). The highest RIs were among the youngest and oldest age

groups: (age group 18 - 24: RI = 23.62, 95% CI = 8.00 - 69.81), (age group ≥ 60: RI = 19.93, 95% CI = 18.75 - 21.17).

Cardiac-related deaths by age group, vaccination type, and sex following vaccination

To determine which group may be driving the increased risk of cardiac-related deaths following vaccination, the vaccination analysis was further stratified by sex, vaccination type, and age groups. Tables 2 and 3 present the sex specific results for cardiac-related deaths following vaccination stratified by age group and vaccination type. Risk was significantly higher during the risk period for males (RI = 1.09, 95% CI = 1.03 - 1.15) but not for females (RI = 1.05, 95% CI = 0.98 - 1.11). Concerning vaccination type, males receiving mRNA vaccination had significantly higher risk (RI = 1.11, 95% CI = 1.05 - 1.18), while males receiving vaccinations that were not mRNA/unknown had significantly lower risk (RI = 0.75, 95% CI = 0.58 - 0.98). RIs for females stratified by vaccination type revealed a similar pattern, with lower, non-significant estimates. Among the subgroups evaluated, males aged 18 - 39 had the highest risk (RI = 1.97, 95% CI = 1.16 - 3.35).

Conclusion

In this statewide study of vaccinated Florida residents aged 18 years or older, COVID-vaccination was not associated with an elevated risk for all-cause mortality. COVID-19 vaccination was associated with a small increased risk for cardiac-related mortality 28 days following vaccination. Results from the stratified analysis for cardiac-related death following vaccination suggests mRNA vaccination may be driving the increased risk in males, especially among males aged 18 - 39. Risk for both all-cause and cardiac-related deaths was substantially higher 28 days following COVID-19 infection. The small risk associated with mRNA vaccination should be balanced against the much larger risk associated with COVID-19 infection.

Table 1: Relative incidence following COVID-19 vaccination or infection for all-cause and cardiac-related deaths during the risk period vs baseline period

	COVID-19 vaccination			COVID-19 infection		
	All-cause deaths			All-cause deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18						
Baseline period	50947	8912.17	Ref	8596	6366.28	Ref
Risk period	9680	1697.56	0.98 (0.95 - 1.00)	34712	1212.62	16.40 (15.99 - 16.83)
18 - 24*						
Baseline period	47	7.94	Ref	19	16.02	Ref
Risk period	7	1.51	0.78 (0.35 - 1.73)	90	3.05	16.58 (9.43 - 29.14)
25 - 39						
Baseline period	397	67.77	Ref	296	160.67	Ref
Risk period	64	12.91	0.84 (0.63 - 1.11)	797	30.60	8.91 (7.59 - 10.47)
40 - 59						
Baseline period	3744	651.06	Ref	1912	1003.86	Ref
Risk period	685	124.01	0.97 (0.89 - 1.06)	4917	191.21	9.38 (8.83 - 9.97)
≥ 60						
Baseline period	46759	8185.40	Ref	6369	5185.72	Ref
Risk period	8924	1559.12	0.97 (0.94 - 0.99)	28908	987.76	18.60 (18.07 - 19.16)
	Cardiac-related deaths			Cardiac-related deaths		
≥ 18						
Baseline period	16406	2923.10	Ref	1819	1450.60	Ref
Risk period	3479	556.78	1.07 (1.03 - 1.12)	8049	276.30	18.24 (17.27 - 19.26)
18 - 24*						
Baseline period	17	3.23	Ref	4	3.23	Ref
Risk period	5	0.62	1.54 (0.57 - 4.19)	18	0.62	23.62 (8.00 - 69.81)
25 - 39						
Baseline period	75	15.29	Ref	47	33.66	Ref
Risk period	29	2.91	2.16 (1.35 - 3.47)	182	6.41	15.39 (10.28 - 23.04)
40 - 59						
Baseline period	1034	183.46	Ref	337	194.33	Ref
Risk period	214	34.94	1.07 (0.91 - 1.26)	985	37.02	10.73 (9.34 - 12.32)
≥ 60						
Baseline period	15280	2721.12	Ref	1431	1219.34	Ref
Risk period	3231	518.31	1.05 (1.01 - 1.10)	6864	232.26	19.93 (18.75 - 21.17)

*Crude due to sparse data

Table 2: Relative incidence of cardiac-related deaths following COVID-19 vaccination for males by age group and vaccination type†

	Cardiac-related deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, male			
Baseline period	8901	1586.72	Ref
Risk period	1893	302.23	1.09 (1.03 - 1.15)
≥ 18, male, mRNA			
Baseline period	8223	1474.12	Ref
Risk period	1805	280.78	1.11 (1.05 - 1.18)
≥ 18, male, not mRNA\unknown			
Baseline period	678	112.60	Ref
Risk period	88	21.45	0.75 (0.58 - 0.98)
18-39, male			
Baseline period	55	11.32	Ref
Risk period	22	2.16	1.97 (1.16 - 3.35)
18-39, male, mRNA			
Baseline period	52	10.58	Ref
Risk period	20	2.02	1.84 (1.05 - 3.21)
40-59, male			
Baseline period	683	120.10	Ref
Risk period	134	22.88	0.98 (0.80 - 1.20)
40-59, male, mRNA			
Baseline period	591	104.81	Ref
Risk period	122	19.96	1.00 (0.81 - 1.24)
40-59, male, not mRNA\unknown*			
Baseline period	92	15.29	Ref
Risk period	12	2.91	0.68 (0.38 - 1.25)
≥ 60, male			
Baseline period	8163	1455.3	Ref
Risk period	1737	277.2	1.08 (1.02 - 1.14)
≥ 60, male, mRNA			
Baseline period	7580	1358.72	Ref
Risk period	1663	258.80	1.10 (1.03 - 1.17)
≥ 60, male, not mRNA\unknown			
Baseline period	583	96.58	Ref
Risk period	74	18.40	0.73 (0.55 - 0.97)

*Crude due to sparse data

†Group 18-39, male, not mRNA\unknown not included due to small sample size (n = 5)

Table 3: Relative incidence of cardiac-related deaths following COVID-19 vaccination for females by age group and vaccination type†

Cardiac-related deaths			
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, female			
Baseline period	7505	1336.38	Ref
Risk period	1586	254.55	1.05 (0.98 - 1.11)
≥ 18, female, mRNA			
Baseline period	6992	1251.41	Ref
Risk period	1521	238.36	1.06 (1.00 - 1.13)
≥ 18, female, not mRNA\unknown			
Baseline period	513	16.18	Ref
Risk period	65	84.97	0.86 (0.63 - 1.17)
18-39, female*			
Baseline period	37	7.20	Ref
Risk period	12	1.37	1.70 (0.89 - 3.27)
18-39, female, mRNA*			
Baseline period	33	6.32	Ref
Risk period	10	1.20	1.59 (0.78 - 3.23)
40-59, female			
Baseline period	351	63.36	Ref
Risk period	80	12.07	1.25 (0.96 - 1.63)
40-59, female, mRNA			
Baseline period	324	58.36	Ref
Risk period	73	11.12	1.25 (0.95 - 1.64)
40-59, female, not mRNA\unknown*			
Baseline period	27	5.00	Ref
Risk period	7	0.95	1.36 (0.59 - 3.13)
≥ 60, female			
Baseline period	7117	1265.82	Ref
Risk period	1494	241.11	1.02 (0.96 - 1.09)
≥ 60, female, mRNA			
Baseline period	6635	1186.73	Ref
Risk period	1438	226.04	1.04 (0.97 - 1.11)
≥ 60, female, not mRNA\unknown			
Baseline period	482	79.09	Ref
Risk period	56	15.06	0.79 (0.57 - 1.10)

*Crude due to sparse data

†Group 18-39, female, not mRNA\unknown not included due to small sample size (n = 6)

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Exploring the relationship between all-cause and cardiac-related mortality following COVID-19 vaccination or infection in Florida residents: a self-controlled case series study

Objective

To evaluate the risks of all-cause and cardiac-related mortality following COVID-19 vaccination.

Methods

Design

The self-controlled case series (SCCS) method adapted to evaluate death as the outcome was used.[1,2] The SCCS method, originally developed to assess vaccine safety, utilizes within-person comparisons to estimate the temporal association between a transient exposure and an acute event.[1] The SCCS method estimates relative incidence (RI) by comparing incidence during a defined high-risk period following exposure with incidence during a control period (i.e., all time in the follow-up period that is not the risk period).[1–4] A major strength of the SCCS method is that fixed-time confounders, such as health related risk-factors, are controlled for.[1,3]

The primary analysis utilized the SCCS method developed for single exposures that cannot be repeated.[1,3,4] Since mRNA vaccinations require a multidose schedule, a simple modification was employed, where the last vaccination preceding death was used as the single exposure.[2] In this method, the within-individual comparison is between the immediate post-exposure period and later post-exposure periods.[3]

While this method has been used to assess risk of death following COVID-19 vaccination,[2] it violates the assumption that an event does not affect subsequent exposure (for mRNA vaccines), which may introduce bias upwards.[5] Further, it does not consider the multidose vaccination schedule required for mRNA vaccination. Thus, a sensitivity analysis was performed using the SCCS method for event-dependent exposures for terminal events.[6–8] This method uses unbiased estimating equations to calculate the RI for multidose vaccines adjusting for age effects.[7–9] The sensitivity analysis was restricted to subgroups that were considered statistically significant in the primary analysis.

Data sources

Data from Florida's reportable disease repository (Merlin), Florida State Health Online Tracking System (FLSHOTS), and death records data from vital statistics were linked.

Setting and study population

For the primary analysis, Florida residents aged 18 years or older who died within 25-weeks of COVID-19 vaccination since the start of the vaccination roll-out (December 15, 2020) were included. For the sensitivity analysis, eligible participants were all Florida residents unvaccinated or vaccinated with mRNA vaccine,[6] aged 18 years or older, who died during the study period (December 15, 2020 - June 1, 2022).

Individuals were excluded if they (1) had a documented COVID-19 infection, (2) experienced a COVID-19 associated death, (3) received a booster, or (4) received their last COVID-19 vaccination after December

8, 2021 (to ensure each individual had the 25-week follow-up period to experience the event of interest).

To allow for death registration, the study end date for both analyses was June 1, 2022.

Exposure and outcomes

The exposure of interest was the 28-day risk period following COVID-19 vaccination. For the sensitivity analysis, participants that had less than 28 days between vaccinations had the risk period following the first dose truncated.

Two outcomes were assessed. Natural all-cause deaths (i.e., excluding homicides, suicides, and accidents) and cardiac-related deaths. Cardiac-related deaths were included if their death record contained an ICD-10 code of I30-I52. For the primary analysis, only participants that experienced the exposure and outcome were included in this study. For the sensitivity analysis, unvaccinated individuals were included to estimate age effects.[6]

Statistical analysis

Primary Analyses

Follow-up began on the day of their last COVID-19 vaccination. Participants were not censored upon death, rather, they were followed for the entire 25-week follow-up period.[1–4]

Conditional logistic regression models offsetting by interval-length were used to estimate RIs and 95% confidence intervals (CIs) comparing incidence in the 28-day risk period to incidence in the baseline period (i.e., the rest of the follow-up period).[2,10] Seasonality was controlled for in each model unless the sample size was too small. Potential confounding by age was reduced by limiting the follow-up period to 25-weeks. Separate models were fitted for each outcome and subgroup analyzed. Estimates were considered statistically significant if the 95% CI did not contain 1.

Data were formatted into a stacked dataset, where exposures for each individual are stacked in columns (i.e., multiple rows per individual), using the SCCS package in R. Conditional logistic regression models were estimated using the clogit function from the survival package.

Sensitivity Analysis

Follow-up began on December 15, 2020 and ended on June 1, 2022. Participants were followed for the entire observation period, regardless of death.[6] Unvaccinated participants were included to estimate age effects.[6,8,9] Unbiased estimating equations were used to calculate the RI for each dose adjusting for age effects.[7–9] Vaccination day (day 0) was specified as a separate risk period to ensure it was not included in the baseline to avoid introducing bias.[6,9] An additional sensitivity analyses was performed using the event-dependent exposure method restricted to vaccinated cases, where follow-up began on exposure date.[8] Results were similar to the method including unvaccinated individuals. Therefore, only the results from the method including unvaccinated individuals are presented.

The analysis was performed using the event-dependent exposure function from the SCCS package in R. The sensitivity analysis was restricted to subgroups that were considered statistically significant in the primary analysis. Estimates were considered statistically significant if the 95% CI did not contain 1.

Results

Primary Analysis

Table 1 presents the results for the primary analysis for natural all-cause and cardiac-related deaths following COVID-19 vaccination.

All-cause deaths following vaccination

In the 28 days following vaccination, no increase in risk was observed for all-cause deaths. A statistically significant decrease was observed for participants 60 years or older in the 28 days following vaccination (RI = 0.97, 95% CI = 0.94 - 0.99).

Cardiac-related deaths following vaccination

In the 28 days following vaccination, a statistically significant increase in cardiac-related deaths was detected for the entire study population (RI = 1.07, 95% CI = 1.03 - 1.12). Stratifying by age group revealed RIs were significantly higher for age groups 25 - 39 (RI = 2.16, 95% CI = 1.35 - 3.47) and 60 or older (RI = 1.05, 95% CI = 1.01 - 1.10). The remaining age groups failed to reach statistical significance.

Cardiac-related deaths by age group, vaccination type, and sex following vaccination

To determine which group may be driving the increased risk of cardiac-related deaths in the primary analysis, the vaccination analysis was further stratified by sex, vaccination type, and age groups. Tables 2 and 3 present the sex specific results for cardiac-related deaths following vaccination stratified by age group and vaccination type. Risk was significantly higher during the risk period for males (RI = 1.09, 95% CI = 1.03 - 1.15) but not for females (RI = 1.05, 95% CI = 0.98 - 1.11). Concerning vaccination type, males receiving mRNA vaccination had significantly higher risk (RI = 1.11, 95% CI = 1.05 - 1.18), while males receiving vaccinations that were not mRNA/unknown had significantly lower risk (RI = 0.75, 95% CI = 0.58 - 0.98). RIs for females stratified by vaccination type revealed a similar pattern, with lower, non-significant estimates. Among the subgroups evaluated, males aged 18 - 39 had the highest risk (RI = 1.97, 95% CI = 1.16 - 3.35).

Sensitivity analysis (subgroups considered statistically significant in the primary analysis)

Using the event-dependent exposures method attenuated the RI estimate for each of the subgroups analyzed for cardiac-related deaths. For the risk-period following either dose, no significant increased risk was found: the RI for the entire study population for the first dose was 0.76 (95% CI = 0.59 - 0.97) and for the second dose, 0.87 (95% CI = 0.69 - 1.10); for age group 25 - 39 for the first dose, 1.08 (95% CI = 0.64 - 1.84) and for the second dose, 1.31 (95% CI = 0.77 - 2.21); for age group 60 or older for the first dose, 0.73 (95% CI = 0.61 - 0.87) and for the second dose, 0.77 (95% CI = 0.65 - 0.92); for males for the first dose, 0.79 (95% CI = 0.61 - 1.01) and for the second dose, 0.89 (95% CI = 0.69 - 1.14); for males 18 - 39 for the first dose, 0.90 (95% CI = 0.48 - 1.71) and for the second dose, 1.14 (95% CI = 0.59 - 2.15); and for males 60 or older for the first dose, 0.72 (95% CI = 0.56 - 0.92) and for the second dose 0.87 (95% CI = 0.69 - 1.11).

Discussion/Conclusion

In this statewide study of vaccinated Florida residents aged 18 years or older, COVID-vaccination was not associated with an elevated risk for all-cause mortality. COVID-19 vaccination was associated with a

slight increased risk for cardiac-related mortality 28 days following vaccination in the primary analysis, but this association was attenuated and no longer significant when applying the event-dependent exposures model utilized for multidose vaccines. Thus, there is little suggestion of any effect immediately following vaccination.

Risk .

Limitations

This study cannot determine the causative nature of a participant's death. We used death certificate data and not medical records. COVID testing status was unknown for those who did not die of/with COVID. Cardiac-related deaths were ascertained if an ACME code of I3-I52 were on their death certificate, thus, the underlying cause of death may not be cardiac-related. This study used surveillance data not intended to answer this specific research question. Further, since mRNA vaccination has been associated with an increase in cardiac events, we may have observed a clustering of cardiac-related comorbidities following vaccination rather than an increase in deaths due to cardiac events.

Limitations specific to primary analysis

Increased risk in the primary analysis for the 25 - 39 age group was based on a small sample size, thus estimates should be interpreted with caution. Confounding by age may be present in the 60 years or older age group, which may explain the slight elevated risk for cardiac-related deaths following vaccination. This may also explain the increased risk for the entire vaccination analysis group for cardiac-related deaths since this group comprises the vast majority of deaths. Removing those aged 60 years or older yielded non-significant results for cardiac-related deaths following vaccination (RI = 1.15, 95% CI = 0.99 - 1.34), mRNA vaccination (RI = 1.17, 95% CI = 1.00 - 1.37), and males with mRNA vaccination (RI = 1.09, 95% CI = 0.89 - 1.34). Future research is needed to better understand the relationship between COVID-19 vaccination and cardiac-related mortality.

- results similar to Janssen now, which makes sense since the primary analysis is meant for single dose vaccinations

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Table 1: Relative incidence following COVID-19 vaccination or infection for all-cause and cardiac-related deaths during the risk period vs baseline period

Subgroup, exposure	No. events	Follow-up, 1000 person days	RI (95% CI)
COVID-19 vaccination			
All-cause deaths			
≥ 18			
Baseline period	50947	8912.17	Ref
Risk period	9680	1697.56	0.98 (0.95 - 1.00)
18 - 24*			
Baseline period	47	7.94	Ref
Risk period	7	1.51	0.78 (0.35 - 1.73)
25 - 39			
Baseline period	397	67.77	Ref
Risk period	64	12.91	0.84 (0.63 - 1.11)
40 - 59			
Baseline period	3744	651.06	Ref
Risk period	685	124.01	0.97 (0.89 - 1.06)
≥ 60			
Baseline period	46759	8185.40	Ref
Risk period	8924	1559.12	0.97 (0.94 - 0.99)
Cardiac-related deaths			
≥ 18			
Baseline period	16406	2923.10	Ref
Risk period	3479	556.78	1.07 (1.03 - 1.12)
18 - 24*			
Baseline period	17	3.23	Ref
Risk period	5	0.62	1.54 (0.57 - 4.19)
25 - 39			
Baseline period	75	15.29	Ref
Risk period	29	2.91	2.16 (1.35 - 3.47)
40 - 59			
Baseline period	1034	183.46	Ref
Risk period	214	34.94	1.07 (0.91 - 1.26)
≥ 60			
Baseline period	15280	2721.12	Ref
Risk period	3231	518.31	1.05 (1.01 - 1.10)

*Crude due to sparse data

Table 2: Relative incidence of cardiac-related deaths following COVID-19 vaccination for males by age group and vaccination type†

	Cardiac-related deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, male			
Baseline period	8901	1586.72	Ref
Risk period	1893	302.23	1.09 (1.03 - 1.15)
≥ 18, male, mRNA			
Baseline period	8223	1474.12	Ref
Risk period	1805	280.78	1.11 (1.05 - 1.18)
≥ 18, male, not mRNA\unknown			
Baseline period	678	112.60	Ref
Risk period	88	21.45	0.75 (0.58 - 0.98)
18-39, male			
Baseline period	55	11.32	Ref
Risk period	22	2.16	1.97 (1.16 - 3.35)
18-39, male, mRNA			
Baseline period	52	10.58	Ref
Risk period	20	2.02	1.84 (1.05 - 3.21)
40-59, male			
Baseline period	683	120.10	Ref
Risk period	134	22.88	0.98 (0.80 - 1.20)
40-59, male, mRNA			
Baseline period	591	104.81	Ref
Risk period	122	19.96	1.00 (0.81 - 1.24)
40-59, male, not mRNA\unknown*			
Baseline period	92	15.29	Ref
Risk period	12	2.91	0.68 (0.38 - 1.25)
≥ 60, male			
Baseline period	8163	1455.3	Ref
Risk period	1737	277.2	1.08 (1.02 - 1.14)
≥ 60, male, mRNA			
Baseline period	7580	1358.72	Ref
Risk period	1663	258.80	1.10 (1.03 - 1.17)
≥ 60, male, not mRNA\unknown			
Baseline period	583	96.58	Ref
Risk period	74	18.40	0.73 (0.55 - 0.97)

*Crude due to sparse data

†Group 18-39, male, not mRNA\unknown not included due to small sample size (n = 5)

Table 3: Relative incidence of cardiac-related deaths following COVID-19 vaccination for females by age group and vaccination type†

	Cardiac-related deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, female			
Baseline period	7505	1336.38	Ref
Risk period	1586	254.55	1.05 (0.98 - 1.11)
≥ 18, female, mRNA			
Baseline period	6992	1251.41	Ref
Risk period	1521	238.36	1.06 (1.00 - 1.13)
≥ 18, female, not mRNA\unknown			
Baseline period	513	16.18	Ref
Risk period	65	84.97	0.86 (0.63 - 1.17)
18-39, female*			
Baseline period	37	7.20	Ref
Risk period	12	1.37	1.70 (0.89 - 3.27)
18-39, female, mRNA*			
Baseline period	33	6.32	Ref
Risk period	10	1.20	1.59 (0.78 - 3.23)
40-59, female			
Baseline period	351	63.36	Ref
Risk period	80	12.07	1.25 (0.96 - 1.63)
40-59, female, mRNA			
Baseline period	324	58.36	Ref
Risk period	73	11.12	1.25 (0.95 - 1.64)
40-59, female, not mRNA\unknown*			
Baseline period	27	5.00	Ref
Risk period	7	0.95	1.36 (0.59 - 3.13)
≥ 60, female			
Baseline period	7117	1265.82	Ref
Risk period	1494	241.11	1.02 (0.96 - 1.09)
≥ 60, female, mRNA			
Baseline period	6635	1186.73	Ref
Risk period	1438	226.04	1.04 (0.97 - 1.11)
≥ 60, female, not mRNA\unknown			
Baseline period	482	79.09	Ref
Risk period	56	15.06	0.79 (0.57 - 1.10)

*Crude due to sparse data

†Group 18-39, female, not mRNA\unknown not included due to small sample size (n = 6)

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Exploring the relationship between all-cause and cardiac-related mortality following COVID-19 vaccination or infection in Florida residents: a self-controlled case series study

Objective

To evaluate the risks of all-cause and cardiac-related mortality following COVID-19 vaccination.

Methods

Design

The self-controlled case series (SCCS) method adapted to evaluate death as the outcome was used.[1,2] The SCCS method, originally developed to assess vaccine safety, utilizes within-person comparisons to estimate the temporal association between a transient exposure and an acute event.[1] The SCCS method estimates relative incidence (RI) by comparing incidence during a defined high-risk period following exposure with incidence during a control period (i.e., all time in the follow-up period that is not the risk period).[1–4] A major strength of the SCCS method is that fixed-time confounders, such as health related risk-factors, are controlled for.[1,3]

The primary analysis utilized the SCCS method developed for single exposures that cannot be repeated.[1,3,4] Since mRNA vaccinations require a multidose schedule, a simple modification was employed, where the last vaccination preceding death was used as the single exposure.[2] In this method, the within-individual comparison is between the immediate post-exposure period and later post-exposure periods.[3]

While this method has been used to assess risk of death following COVID-19 vaccination,[2] it violates the assumption that an event does not affect subsequent exposure (for mRNA vaccines), which may introduce bias upwards.[5] Further, it does not consider the multidose vaccination schedule required for mRNA vaccination. Thus, a sensitivity analysis was performed using the SCCS method for event-dependent exposures for terminal events.[6–8] This method uses unbiased estimating equations to calculate the RI for multidose vaccines adjusting for age effects.[7–9] The sensitivity analysis was restricted to subgroups that were considered statistically significant in the primary analysis.

Data sources

Data from Florida's reportable disease repository (Merlin), Florida State Health Online Tracking System (FLSHOTS), and death records data from vital statistics were linked.

Setting and study population

For the primary analysis, Florida residents aged 18 years or older who died within 25-weeks of COVID-19 vaccination since the start of the vaccination roll-out (December 15, 2020) were included. For the sensitivity analysis, eligible participants were all Florida residents unvaccinated or vaccinated with mRNA vaccine,[6] aged 18 years or older, who died during the study period (December 15, 2020 - June 1, 2022).

Individuals were excluded if they (1) had a documented COVID-19 infection, (2) experienced a COVID-19 associated death, (3) received a booster, or (4) received their last COVID-19 vaccination after December

8, 2021 (to ensure each individual had the 25-week follow-up period to experience the event of interest).

To allow for death registration, the study end date for both analyses was June 1, 2022.

Exposure and outcomes

The exposure of interest was the 28-day risk period following COVID-19 vaccination. For the sensitivity analysis, participants that had less than 28 days between vaccinations had the risk period following the first dose truncated.

Two outcomes were assessed. Natural all-cause deaths (i.e., excluding homicides, suicides, and accidents) and cardiac-related deaths. Cardiac-related deaths were included if their death record contained an ICD-10 code of I30-I52. For the primary analysis, only participants that experienced the exposure and outcome were included in this study. For the sensitivity analysis, unvaccinated individuals were included to estimate age effects.[6]

Statistical analysis

Primary Analyses

Follow-up began on the day of their last COVID-19 vaccination. Participants were not censored upon death, rather, they were followed for the entire 25-week follow-up period.[1–4]

Conditional logistic regression models offsetting by interval-length were used to estimate RIs and 95% confidence intervals (CIs) comparing incidence in the 28-day risk period to incidence in the baseline period (i.e., the rest of the follow-up period).[2,10] Seasonality was controlled for in each model unless the sample size was too small. Potential confounding by age was reduced by limiting the follow-up period to 25-weeks. Separate models were fitted for each outcome and subgroup analyzed. Estimates were considered statistically significant if the 95% CI did not contain 1.

Data were formatted into a stacked dataset, where exposures for each individual are stacked in columns (i.e., multiple rows per individual), using the SCCS package in R. Conditional logistic regression models were estimated using the clogit function from the survival package.

Sensitivity Analysis

Follow-up began on December 15, 2020 and ended on June 1, 2022. Participants were followed for the entire observation period, regardless of death.[6] Unvaccinated participants were included to estimate age effects.[6,8,9] Unbiased estimating equations were used to calculate the RI for each dose adjusting for age effects.[7–9] Vaccination day (day 0) was specified as a separate risk period to ensure it was not included in the baseline to avoid introducing bias.[6,9] An additional sensitivity analyses was performed using the event-dependent exposure method restricted to vaccinated cases, where follow-up began on exposure date.[8] Results were similar to the method including unvaccinated individuals. Therefore, only the results from the method including unvaccinated individuals are presented.

The analysis was performed using the event-dependent exposure function from the SCCS package in R. The sensitivity analysis was restricted to subgroups that were considered statistically significant in the primary analysis. Estimates were considered statistically significant if the 95% CI did not contain 1.

Results

Primary Analysis

Table 1 presents the results for the primary analysis for natural all-cause and cardiac-related deaths following COVID-19 vaccination.

All-cause deaths following vaccination

In the 28 days following vaccination, no increase in risk was observed for all-cause deaths. A statistically significant decrease was observed for participants 60 years or older in the 28 days following vaccination (RI = 0.97, 95% CI = 0.94 - 0.99).

Cardiac-related deaths following vaccination

In the 28 days following vaccination, a statistically significant increase in cardiac-related deaths was detected for the entire study population (RI = 1.07, 95% CI = 1.03 - 1.12). Stratifying by age group revealed RIs were significantly higher for age groups 25 - 39 (RI = 2.16, 95% CI = 1.35 - 3.47) and 60 or older (RI = 1.05, 95% CI = 1.01 - 1.10). The remaining age groups failed to reach statistical significance.

Cardiac-related deaths by age group, vaccination type, and sex following vaccination

To determine which group may be driving the increased risk of cardiac-related deaths in the primary analysis, the vaccination analysis was further stratified by sex, vaccination type, and age groups. Tables 2 and 3 present the sex specific results for cardiac-related deaths following vaccination stratified by age group and vaccination type. Risk was significantly higher during the risk period for males (RI = 1.09, 95% CI = 1.03 - 1.15) but not for females (RI = 1.05, 95% CI = 0.98 - 1.11). Concerning vaccination type, males receiving mRNA vaccination had significantly higher risk (RI = 1.11, 95% CI = 1.05 - 1.18), while males receiving vaccinations that were not mRNA/unknown had significantly lower risk (RI = 0.75, 95% CI = 0.58 - 0.98). RIs for females stratified by vaccination type revealed a similar pattern, with lower, non-significant estimates. Among the subgroups evaluated, males aged 18 - 39 had the highest risk (RI = 1.97, 95% CI = 1.16 - 3.35).

Sensitivity analysis (subgroups considered statistically significant in the primary analysis)

Using the event-dependent exposures method attenuated the RI estimate for each of the subgroups analyzed for cardiac-related deaths. For the risk-period following either dose, no significant increased risk was found: the RI for the entire study population for the first dose was 0.76 (95% CI = 0.59 - 0.97) and for the second dose, 0.87 (95% CI = 0.69 - 1.10); for age group 25 - 39 for the first dose, 1.08 (95% CI = 0.64 - 1.84) and for the second dose, 1.31 (95% CI = 0.77 - 2.21); for age group 60 or older for the first dose, 0.73 (95% CI = 0.61 - 0.87) and for the second dose, 0.77 (95% CI = 0.65 - 0.92); for males for the first dose, 0.79 (95% CI = 0.61 - 1.01) and for the second dose, 0.89 (95% CI = 0.69 - 1.14); for males 18 - 39 for the first dose, 0.90 (95% CI = 0.48 - 1.71) and for the second dose, 1.14 (95% CI = 0.59 - 2.15); and for males 60 or older for the first dose, 0.72 (95% CI = 0.56 - 0.92) and for the second dose 0.87 (95% CI = 0.69 - 1.11).

Discussion/Conclusion

In this statewide study of vaccinated Florida residents aged 18 years or older, COVID-vaccination was not associated with an elevated risk for all-cause mortality. COVID-19 vaccination was associated with a

slight increased risk for cardiac-related mortality 28 days following vaccination in the primary analysis, but this association was attenuated and no longer significant when applying the event-dependent exposures model utilized for multidose vaccines. Thus, there is little suggestion of any effect immediately following vaccination.

Risk .

Limitations

This study cannot determine the causative nature of a participant's death. We used death certificate data and not medical records. COVID testing status was unknown for those who did not die of/with COVID. Cardiac-related deaths were ascertained if an ACME code of I3-I52 were on their death certificate, thus, the underlying cause of death may not be cardiac-related. This study used surveillance data not intended to answer this specific research question. Further, since mRNA vaccination has been associated with an increase in cardiac events, we may have observed a clustering of cardiac-related comorbidities following vaccination rather than an increase in deaths due to cardiac events.

Limitations specific to primary analysis

Increased risk in the primary analysis for the 25 - 39 age group was based on a small sample size, thus estimates should be interpreted with caution. Confounding by age may be present in the 60 years or older age group, which may explain the slight elevated risk for cardiac-related deaths following vaccination. This may also explain the increased risk for the entire vaccination analysis group for cardiac-related deaths since this group comprises the vast majority of deaths. Removing those aged 60 years or older yielded non-significant results for cardiac-related deaths following vaccination (RI = 1.15, 95% CI = 0.99 - 1.34), mRNA vaccination (RI = 1.17, 95% CI = 1.00 - 1.37), and males with mRNA vaccination (RI = 1.09, 95% CI = 0.89 - 1.34). Future research is needed to better understand the relationship between COVID-19 vaccination and cardiac-related mortality.

- results similar to Janssen now, which makes sense since the primary analysis is meant for single dose vaccinations

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Table 1: Relative incidence following COVID-19 vaccination or infection for all-cause and cardiac-related deaths during the risk period vs baseline period

COVID-19 vaccination			
All-cause deaths			
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18			
Baseline period	50947	8912.17	Ref
Risk period	9680	1697.56	0.98 (0.95 - 1.00)
18 - 24*			
Baseline period	47	7.94	Ref
Risk period	7	1.51	0.78 (0.35 - 1.73)
25 - 39			
Baseline period	397	67.77	Ref
Risk period	64	12.91	0.84 (0.63 - 1.11)
40 - 59			
Baseline period	3744	651.06	Ref
Risk period	685	124.01	0.97 (0.89 - 1.06)
≥ 60			
Baseline period	46759	8185.40	Ref
Risk period	8924	1559.12	0.97 (0.94 - 0.99)
Cardiac-related deaths			
≥ 18			
Baseline period	16406	2923.10	Ref
Risk period	3479	556.78	1.07 (1.03 - 1.12)
18 - 24*			
Baseline period	17	3.23	Ref
Risk period	5	0.62	1.54 (0.57 - 4.19)
25 - 39			
Baseline period	75	15.29	Ref
Risk period	29	2.91	2.16 (1.35 - 3.47)
40 - 59			
Baseline period	1034	183.46	Ref
Risk period	214	34.94	1.07 (0.91 - 1.26)
≥ 60			
Baseline period	15280	2721.12	Ref
Risk period	3231	518.31	1.05 (1.01 - 1.10)

*Crude due to sparse data

Table 2: Relative incidence of cardiac-related deaths following COVID-19 vaccination for males by age group and vaccination type†

	Cardiac-related deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, male			
Baseline period	8901	1586.72	Ref
Risk period	1893	302.23	1.09 (1.03 - 1.15)
≥ 18, male, mRNA			
Baseline period	8223	1474.12	Ref
Risk period	1805	280.78	1.11 (1.05 - 1.18)
≥ 18, male, not mRNA\unknown			
Baseline period	678	112.60	Ref
Risk period	88	21.45	0.75 (0.58 - 0.98)
18-39, male			
Baseline period	55	11.32	Ref
Risk period	22	2.16	1.97 (1.16 - 3.35)
18-39, male, mRNA			
Baseline period	52	10.58	Ref
Risk period	20	2.02	1.84 (1.05 - 3.21)
40-59, male			
Baseline period	683	120.10	Ref
Risk period	134	22.88	0.98 (0.80 - 1.20)
40-59, male, mRNA			
Baseline period	591	104.81	Ref
Risk period	122	19.96	1.00 (0.81 - 1.24)
40-59, male, not mRNA\unknown*			
Baseline period	92	15.29	Ref
Risk period	12	2.91	0.68 (0.38 - 1.25)
≥ 60, male			
Baseline period	8163	1455.3	Ref
Risk period	1737	277.2	1.08 (1.02 - 1.14)
≥ 60, male, mRNA			
Baseline period	7580	1358.72	Ref
Risk period	1663	258.80	1.10 (1.03 - 1.17)
≥ 60, male, not mRNA\unknown			
Baseline period	583	96.58	Ref
Risk period	74	18.40	0.73 (0.55 - 0.97)

*Crude due to sparse data

†Group 18-39, male, not mRNA\unknown not included due to small sample size (n = 5)

Table 3: Relative incidence of cardiac-related deaths following COVID-19 vaccination for females by age group and vaccination type†

	Cardiac-related deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, female			
Baseline period	7505	1336.38	Ref
Risk period	1586	254.55	1.05 (0.98 - 1.11)
≥ 18, female, mRNA			
Baseline period	6992	1251.41	Ref
Risk period	1521	238.36	1.06 (1.00 - 1.13)
≥ 18, female, not mRNA\unknown			
Baseline period	513	16.18	Ref
Risk period	65	84.97	0.86 (0.63 - 1.17)
18-39, female*			
Baseline period	37	7.20	Ref
Risk period	12	1.37	1.70 (0.89 - 3.27)
18-39, female, mRNA*			
Baseline period	33	6.32	Ref
Risk period	10	1.20	1.59 (0.78 - 3.23)
40-59, female			
Baseline period	351	63.36	Ref
Risk period	80	12.07	1.25 (0.96 - 1.63)
40-59, female, mRNA			
Baseline period	324	58.36	Ref
Risk period	73	11.12	1.25 (0.95 - 1.64)
40-59, female, not mRNA\unknown*			
Baseline period	27	5.00	Ref
Risk period	7	0.95	1.36 (0.59 - 3.13)
≥ 60, female			
Baseline period	7117	1265.82	Ref
Risk period	1494	241.11	1.02 (0.96 - 1.09)
≥ 60, female, mRNA			
Baseline period	6635	1186.73	Ref
Risk period	1438	226.04	1.04 (0.97 - 1.11)
≥ 60, female, not mRNA\unknown			
Baseline period	482	79.09	Ref
Risk period	56	15.06	0.79 (0.57 - 1.10)

*Crude due to sparse data

†Group 18-39, female, not mRNA\unknown not included due to small sample size (n = 6)

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Exploring the relationship between all-cause and cardiac-related mortality following COVID-19 vaccination or infection in Florida residents: a self-controlled case series study

Objective

To evaluate the risks of all-cause and cardiac-related mortality following COVID-19 vaccination.

Methods

Design

The self-controlled case series (SCCS) method adapted to evaluate death as the outcome was used.[1,2] The SCCS method, originally developed to assess vaccine safety, utilizes within-person comparisons to estimate the temporal association between a transient exposure and an acute event.[1] The SCCS method estimates relative incidence (RI) by comparing incidence during a defined high-risk period following exposure with incidence during a control period (i.e., all time in the follow-up period that is not the risk period).[1–4] A major strength of the SCCS method is that fixed-time confounders, such as health related risk-factors, are controlled for.[1,3]

The primary analysis utilized the SCCS method developed for single exposures that cannot be repeated.[1,3,4] Since mRNA vaccinations require a multidose schedule, a simple modification was employed, where the last vaccination preceding death was used as the single exposure.[2]

While this method has been used to assess risk of death following COVID-19 vaccination,[2] it violates the assumption that an event does not affect subsequent exposure (for mRNA vaccines), which introduces bias upwards.[5] Further, it does not consider the multidose vaccination schedule required for mRNA vaccination. Thus, a sensitivity analysis was performed using the SCCS method for event-dependent exposures for terminal events.[6–8] This method uses unbiased estimating equations to calculate the RI for multidose vaccines adjusting for age effects.[7–9] The sensitivity analysis was restricted to subgroups that were considered statistically significant in the primary analysis.

Data sources

Data from Florida's reportable disease repository (Merlin), Florida State Health Online Tracking System (FLSHOTS), and death records data from vital statistics were linked.

Setting and study population

For the primary analysis, Florida residents aged 18 years or older who died within 25-weeks of COVID-19 vaccination since the start of the vaccination roll-out (December 15, 2020) were included. For the sensitivity analysis, eligible participants were all Florida residents unvaccinated or vaccinated with mRNA vaccine,[6] aged 18 years or older, who died during the study period (December 15, 2020 - June 1, 2022).

Individuals were excluded if they (1) had a documented COVID-19 infection, (2) experienced a COVID-19 associated death, (3) received a booster, or (4) received their last COVID-19 vaccination after December 8, 2021 (only for primary analysis to ensure each individual had the 25-week follow-up period to experience the event of interest).

To allow for death registration, the study end date for both analyses was June 1, 2022.

Exposure and outcomes

The exposure of interest was the 28-day risk period following COVID-19 vaccination. For the sensitivity analysis, participants that had less than 28 days between vaccinations had the risk period following the first dose truncated.

Two outcomes were assessed. Natural all-cause deaths (i.e., excluding homicides, suicides, and accidents) and cardiac-related deaths. Cardiac-related deaths were included if their death record contained an ICD-10 code of I30-I52. For the primary analysis, only participants that experienced the exposure and outcome were included in this study. For the sensitivity analysis, unvaccinated individuals were included to estimate age effects.[6]

Statistical analysis

Primary Analyses

Follow-up began on the day of their last COVID-19 vaccination. Participants were not censored upon death, rather, they were followed for the entire 25-week follow-up period.[1–4]

Conditional logistic regression models offsetting by interval-length were used to estimate RIs and 95% confidence intervals (CIs) comparing incidence in the 28-day risk period to incidence in the baseline period (i.e., the rest of the follow-up period).[2,10] Seasonality was controlled for in each model unless the sample size was too small. Potential confounding by age was reduced by limiting the follow-up period to 25-weeks. Separate models were fitted for each outcome and subgroup analyzed. Estimates were considered statistically significant if the 95% CI did not contain 1.

Data were formatted into a stacked dataset, where exposures for each individual are stacked in columns (i.e., multiple rows per individual), using the SCCS package in R. Conditional logistic regression models were estimated using the clogit function from the survival package.

Sensitivity Analysis

Follow-up began on December 15, 2020 and ended on June 1, 2022. Participants were followed for the entire observation period, regardless of death.[6] Unvaccinated participants were included to estimate age effects.[6,8,9] Unbiased estimating equations were used to calculate the RI for each dose adjusting for age effects.[7–9] Vaccination day (day 0) was specified as a separate risk period to ensure it was not included in the baseline to avoid introducing bias.[6,9] An additional sensitivity analyses was performed using the event-dependent exposure method restricted to vaccinated cases, where follow-up began on exposure date.[8] Results were similar to the method including unvaccinated individuals. Therefore, only the results from the method including unvaccinated individuals are presented.

The analysis was performed using the event-dependent exposure function from the SCCS package in R. The sensitivity analysis was restricted to subgroups that were considered statistically significant in the primary analysis. Estimates were considered statistically significant if the 95% CI did not contain 1.

Results

Primary Analysis

Table 1 presents the results for the primary analysis for natural all-cause and cardiac-related deaths following COVID-19 vaccination.

All-cause deaths following vaccination

In the 28 days following vaccination, no increase in risk was observed for all-cause deaths. A statistically significant decrease was observed for participants 60 years or older in the 28 days following vaccination (RI = 0.97, 95% CI = 0.94 - 0.99).

Cardiac-related deaths following vaccination

In the 28 days following vaccination, a statistically significant increase in cardiac-related deaths was detected for the entire study population (RI = 1.07, 95% CI = 1.03 - 1.12). Stratifying by age group revealed RIs were significantly higher for age groups 25 - 39 (RI = 2.16, 95% CI = 1.35 - 3.47) and 60 or older (RI = 1.05, 95% CI = 1.01 - 1.10). The remaining age groups failed to reach statistical significance.

Cardiac-related deaths by age group, vaccination type, and sex following vaccination

To determine which group may be driving the increased risk of cardiac-related deaths in the primary analysis, the vaccination analysis was further stratified by sex, vaccination type, and age groups. Tables 2 and 3 present the sex specific results for cardiac-related deaths following vaccination stratified by age group and vaccination type. Risk was significantly higher during the risk period for males (RI = 1.09, 95% CI = 1.03 - 1.15) but not for females (RI = 1.05, 95% CI = 0.98 - 1.11). Concerning vaccination type, males receiving mRNA vaccination had significantly higher risk (RI = 1.11, 95% CI = 1.05 - 1.18), while males receiving vaccinations that were not mRNA/unknown had significantly lower risk (RI = 0.75, 95% CI = 0.58 - 0.98). RIs for females stratified by vaccination type revealed a similar pattern, with lower, non-significant estimates. Among the subgroups evaluated, males aged 18 - 39 had the highest risk (RI = 1.97, 95% CI = 1.16 - 3.35).

Sensitivity analysis (subgroups considered statistically significant in the primary analysis)

Using the event-dependent exposures method attenuated the RI estimate for each of the subgroups analyzed for cardiac-related deaths. For the risk-period following either dose, no significant increased risk was found: the RI for the entire study population for the first dose was 0.76 (95% CI = 0.59 - 0.97) and for the second dose, 0.87 (95% CI = 0.69 - 1.10); for age group 25 - 39 for the first dose, 1.08 (95% CI = 0.64 - 1.84) and for the second dose, 1.31 (95% CI = 0.77 - 2.21); for age group 60 or older for the first dose, 0.73 (95% CI = 0.61 - 0.87) and for the second dose, 0.77 (95% CI = 0.65 - 0.92); for males for the first dose, 0.79 (95% CI = 0.61 - 1.01) and for the second dose, 0.89 (95% CI = 0.69 - 1.14); for males 18 - 39 for the first dose, 0.90 (95% CI = 0.48 - 1.71) and for the second dose, 1.14 (95% CI = 0.59 - 2.15); and for males 60 or older for the first dose, 0.72 (95% CI = 0.56 - 0.92) and for the second dose 0.87 (95% CI = 0.69 - 1.11).

Discussion/Conclusion

In this statewide analysis of vaccinated Florida residents aged 18 years or older, COVID-vaccination was not associated with an elevated risk for all-cause mortality. COVID-19 vaccination was associated with a slight increased risk for cardiac-related mortality 28 days following vaccination in the primary analysis, but this association was attenuated and no longer significant when applying the more appropriate

event-dependent exposures model utilized for multidose vaccines. Thus, there is little suggestion of any effect immediately following vaccination.

The findings from the event-dependent model are similar to other studies that have assessed the association between COVID-19 vaccination and acute cardiovascular events. Multiple studies have reported that mRNA vaccines were not associated with increased risk of severe, acute cardiovascular events including acute myocardial infarction, stroke, and pulmonary embolism following vaccination.[9,11,12] A recent study on non-covid-19 mortality and COVID-19 vaccination found a significantly lower mortality rate for vaccine recipients when compared to their unvaccinated counterparts.[13]

A study assessing the association between COVID-19 infection, vaccination, and cardiac complications found that there was a small increase in myocarditis and pericarditis following mRNA vaccination.[14] The authors also noted that vaccinated-associated myocarditis events have mostly been mild or moderate[15] and confined to the period immediately following vaccination.[14] Using the same population, the authors found a much a higher risk of hospitalization or death from myocarditis, pericarditis, and cardiac arrhythmia following COVID-19 infection.[14]

Conversely, COVID-19 infection has been independently associated with a significant increase in severe, acute cardiovascular events that can increase short-term mortality.[16] It is well established that COVID-19 infection can trigger acute cardiovascular events, and individuals with COVID-19 that have underlying cardiovascular comorbidities are associated with increased mortality.[17,18] Further, an internal analysis similar to the primary analysis using initial, diagnosed COVID-19 infection as the exposure revealed substantial, significant increased risk for all-cause and cardiac-related deaths for every age-group evaluated.

In summary, although results from the primary analysis revealed a small increase in risk following COVID-19 vaccination, the estimates were biased upwards. The results from the event-dependent model that uses unbiased estimating equations adjusted for age yielded non-significant results for each subgroup considered statistically significant in the primary analysis, indicating there is no increased risk for cardiac-mortality following mRNA vaccinations. The risk associated with COVID-19 infection clearly outweighs any potential risk associated with mRNA vaccination.

Limitations

These data are preliminary and based on surveillance data, not academic research, and should be interpreted with caution. The results have several limitations:

This study cannot determine the causative nature of a participant's death. We used death certificate data and not medical records. COVID testing status was unknown for those who did not die of/with COVID. Cardiac-related deaths were ascertained if an ACME code of I3-I52 were on their death certificate, thus, the underlying cause of death may not be cardiac-related. Residual time-varying confounding may be present. The primary analysis used a method that was developed for exposures that cannot be repeated and likely biased estimates upward for all-cause and cardiac-related deaths.

The finding that the Janssen vaccine was protective against mortality within 28 days of vaccination could be due to confounding and needs to be further evaluated. It is likely that the populations who received COVID-19 mRNA vaccine and the Johnson vaccine are different, something we were not able to

ascertain in this analysis. It is possible that the population who received the Johnson vaccine was younger and healthier than those receiving the mRNA vaccines. The Pfizer and Moderna mRNA vaccines were released more than 2 months earlier than the Janssen vaccine when the recommendations were limited to those 65 and older.

Additional studies should be conducted to further understand the risks and benefits of vaccination of males between 25 - 39. Increased risk in the primary analysis for the 25 - 39 age group and males aged 18 - 39 was based on a small sample size, results should be interpreted with caution. Additionally, significant increased mortality from diagnosed COVID-19 infection was substantially higher and occurred among all adult age groups. COVID-19 mortality among asymptomatic or undiagnosed COVID-19 infection is less clear. However, excess overall mortality among 25–44-year-old Americans was significant in a study[1] looking at mortality from January 2020-October 2020. The largest increases were among Hispanic and Latino populations. Since the vaccine is designed to mimic a natural infection, it will be important to better understand what proportion of excess deaths are related to cardiac events that could be attributed to COVID-19 infections before vaccine recommendations are changed.

For the primary analysis, confounding by age may be present in the 60 years or older age group, which may explain the slight elevated risk for cardiac-related deaths following vaccination. This also explains the increased risk for the entire vaccination analysis group for cardiac-related deaths since this group comprises the vast majority of deaths. Removing those aged 60 years or older yielded non-significant results for cardiac-related deaths following vaccination (RI = 1.15, 95% CI = 0.99 - 1.34), mRNA vaccination (RI = 1.17, 95% CI = 1.00 - 1.37), and males with mRNA vaccination (RI = 1.09, 95% CI = 0.89 - 1.34).

Lastly, this analysis was conducted during the first months the vaccines were available. Both COVID-19 mortality due to infection or risk of mortality associated with vaccination have likely changed over time. In the fall of 2022, most people have either been vaccinated or have natural immunity to COVID-19. Many have had multiple vaccine doses, multiple infections or both. Research to assess the current risks and benefits of the COVID-19 vaccine to help update vaccine recommendations should be studied in this context.

[1] https://www.cdc.gov/mmwr/volumes/69/wr/mm6942e2.htm

Table 1: Relative incidence following COVID-19 vaccination or infection for all-cause and cardiac-related deaths during the risk period vs baseline period

COVID-19 vaccination			
All-cause deaths			
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18			
Baseline period	50947	8912.17	Ref
Risk period	9680	1697.56	0.98 (0.95 - 1.00)
18 - 24*			
Baseline period	47	7.94	Ref
Risk period	7	1.51	0.78 (0.35 - 1.73)
25 - 39			
Baseline period	397	67.77	Ref
Risk period	64	12.91	0.84 (0.63 - 1.11)
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Risk period	685	124.01	0.97 (0.89 - 1.06)
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Baseline period	46759	8185.40	Ref
Risk period	8924	1559.12	0.97 (0.94 - 0.99)
Cardiac-related deaths			
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Baseline period	16406	2923.10	Ref
Risk period	3479	556.78	1.07 (1.03 - 1.12)
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Baseline period	17	3.23	Ref
Risk period	5	0.62	1.54 (0.57 - 4.19)
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Baseline period	75	15.29	Ref
Risk period	29	2.91	2.16 (1.35 - 3.47)
40 - 59			
Baseline period	1034	183.46	Ref
Risk period	214	34.94	1.07 (0.91 - 1.26)
≥ 60			
Baseline period	15280	2721.12	Ref
Risk period	3231	518.31	1.05 (1.01 - 1.10)

*Crude due to sparse data

Table 2: Relative incidence of cardiac-related deaths following COVID-19 vaccination for males by age group and vaccination type†

	Cardiac-related deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, male			
Baseline period	8901	1586.72	Ref
Risk period	1893	302.23	1.09 (1.03 - 1.15)
≥ 18, male, mRNA			
Baseline period	8223	1474.12	Ref
Risk period	1805	280.78	1.11 (1.05 - 1.18)
≥ 18, male, not mRNA\unknown			
Baseline period	678	112.60	Ref
Risk period	88	21.45	0.75 (0.58 - 0.98)
18-39, male			
Baseline period	55	11.32	Ref
Risk period	22	2.16	1.97 (1.16 - 3.35)
18-39, male, mRNA			
Baseline period	52	10.58	Ref
Risk period	20	2.02	1.84 (1.05 - 3.21)
40-59, male			
Baseline period	683	120.10	Ref
Risk period	134	22.88	0.98 (0.80 - 1.20)
40-59, male, mRNA			
Baseline period	591	104.81	Ref
Risk period	122	19.96	1.00 (0.81 - 1.24)
40-59, male, not mRNA\unknown*			
Baseline period	92	15.29	Ref
Risk period	12	2.91	0.68 (0.38 - 1.25)
≥ 60, male			
Baseline period	8163	1455.3	Ref
Risk period	1737	277.2	1.08 (1.02 - 1.14)
≥ 60, male, mRNA			
Baseline period	7580	1358.72	Ref
Risk period	1663	258.80	1.10 (1.03 - 1.17)
≥ 60, male, not mRNA\unknown			
Baseline period	583	96.58	Ref
Risk period	74	18.40	0.73 (0.55 - 0.97)

*Crude due to sparse data

†Group 18-39, male, not mRNA\unknown not included due to small sample size (n = 5)

Table 3: Relative incidence of cardiac-related deaths following COVID-19 vaccination for females by age group and vaccination type†

	Cardiac-related deaths		
Subgroup, exposure	**No. events**	**Follow-up, 1000 person days**	**RI (95% CI)**
≥ 18, female			
Baseline period	7505	1336.38	Ref
Risk period	1586	254.55	1.05 (0.98 - 1.11)
≥ 18, female, mRNA			
Baseline period	6992	1251.41	Ref
Risk period	1521	238.36	1.06 (1.00 - 1.13)
≥ 18, female, not mRNA\unknown			
Baseline period	513	16.18	Ref
Risk period	65	84.97	0.86 (0.63 - 1.17)
18-39, female*			
Baseline period	37	7.20	Ref
Risk period	12	1.37	1.70 (0.89 - 3.27)
18-39, female, mRNA*			
Baseline period	33	6.32	Ref
Risk period	10	1.20	1.59 (0.78 - 3.23)
40-59, female			
Baseline period	351	63.36	Ref
Risk period	80	12.07	1.25 (0.96 - 1.63)
40-59, female, mRNA			
Baseline period	324	58.36	Ref
Risk period	73	11.12	1.25 (0.95 - 1.64)
40-59, female, not mRNA\unknown*			
Baseline period	27	5.00	Ref
Risk period	7	0.95	1.36 (0.59 - 3.13)
≥ 60, female			
Baseline period	7117	1265.82	Ref
Risk period	1494	241.11	1.02 (0.96 - 1.09)
≥ 60, female, mRNA			
Baseline period	6635	1186.73	Ref
Risk period	1438	226.04	1.04 (0.97 - 1.11)
≥ 60, female, not mRNA\unknown			
Baseline period	482	79.09	Ref
Risk period	56	15.06	0.79 (0.57 - 1.10)

*Crude due to sparse data

†Group 18-39, female, not mRNA\unknown not included due to small sample size (n = 6)

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